ADRENALECTOMY IN CUSHING'S SYNDROME

MANAGEMENT AND METABOLIC ASPECTS

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Cushing's syndrome is a progressive fatal disease with an average duration of five years (Sprague 1953, Plotz et al. 1952). The underlying metabolic disturbance is due to excessive secretion of adrenocortical hormones, but the anatomical lesion of the adrenal glands may be a tumour or bilateral hyperplasia. Early attempts to control the activity of hyperplastic adrenals by resection proved disappointing.

Cushing's syndrome was ameliorated but not abolished by the removal of one adrenal, and more extensive resection was too dangerous in the absence of adequate hormonal therapy (Cope and Raker 1955). However, the introduction of cortisone and hydrocortisone made it possible for patients to survive radical subtotal or even total adrenalectomy. Many workers have recorded the abolition of Cushing's syndrome by the removal of at least 80% of adrenal tissue (Sprague 1953, Bishop et al. 1954, Beck et al. 1954, Coone and Humphreys 1956, Mason 1957). Hernberg (1954) suggested extensive subtotal resection of both adrenals. Bishop et al. (1954) and Montgomery and Wellbourn (1957) favour complete removal of one adrenal and, at a later date, resection of the remaining gland. However, Poutasse and Higgins (1953) considered that both adrenals should be resected at one operation, and if the disease was severe no adrenal tissue should be left.

We describe here our experience with adrenalectomy in the treatment of Cushing's syndrome associated with bilateral adrenal hyperplasia, and outline the therapeutic regime which we favour. The data on serum-electrolytes and glucose tolerance are drawn from 17 patients with adrenal hyperplasia and 1 patient with Cushing's syndrome due to an adrenal carcinoma on whom special metabolic observations were made (case 1). Special metabolic studies, including nitrogen and potassium balances, were made before operation in 8 patients and after adrenalectomy in 9 instances.

Diagnosis

Adrenalectomy, with its immediate dangers and prospect of permanent adrenal hypofunction, should be undertaken only when the diagnosis of Cushing's syndrome is proved beyond doubt. First, difficulty may be encountered in adolescent girls who exhibit obesity, acne, pink striæ distensæ, menstrual irregularity, and even a slight rise in blood-pressure. There may be some increase in the urinary metabolites of hydrocortisone, indicating hyperactive adrenal function; but the absence of muscle wasting and the presence of generalised obesity help to distinguish this from Cushing's syndrome. It is essential to observe these patients, rather than to submit them to unnecessary operation, as the disturbance is transitory and responds to a reducing diet. A similar type of benign transient disturbance is sometimes seen in young men. In contrast to these conditions, which represent a minor deviation of endocrine physiology, is the adrenogenital syndrome in women, arising in puberty and continuing throughout life. Such patients are plethoric, hirsute obese yet muscular, with irregular menstruation and, in later years, benign hypertension. Urinary steroid excretion is increased, but this is mainly in the form of 17-ketosteroids. However disfiguring the disease, it is not progressive or fatal, and therefore in our view adrenalectomy is seldom justified.

The diagnosis of Cushing's syndrome requires investigation of both the disorder of function and the anatomical lesion. The disturbance of physiology is apparent from the clinical features. The effect of increased protein catabolism (or failure of anabolism) can be directly estimated by a nitrogen balance, but this is not essential. Associated metabolic changes equally can be detected by the glucose-tolerance test and radiographic examination of bones (particularly the spine and ribs) for evidence of osteoporosis; spontaneous fracture of osteoporotic bone, especially in the ribs, is common. Electrolyte disturbance must be investigated by estimation of serum sodium, chloride, potassium, and bicarbonate. Because the electrolyte equilibrium is unstable in Cushing's syndrome, a single reading is unreliable and therefore serum-electrolytes should be measured on several occasions. An electrocardiogram provides confirmatory evidence of potassium depletion. The diagnostic significance of these metabolic changes will be discussed later.

Hypertension is an important feature in prognosis, and requires careful assessment by repeated estimations of the blood-pressure with the patient at rest. Full renal function tests, including estimations of blood-urea, creatinine clearance, and urinary urea concentration, should be carried out.

Estimation of urinary 17-ketogenic steroids by the method of Norymberski et al. (1953) has proved satisfactory, and by this method distinctly raised values were found in all our cases of Cushing's syndrome. Nabarro et al. (1957) were equally impressed by Norymberski's modified method (Appleby et al. 1955) which measures 17-hydroxycorticosteroids. Both these methods, however, measure other substances which are not derived from hydrocortisone, particularly steroids with 17·20-diol or 21-deoxyketol types of side chain which are excreted in large quantities in adrenal virilism. Hence high values recorded by these methods are not specific for Cushing's syndrome. The determination of 17-hydroxycorticoids by the Porter-Silber reaction, according to the method of Reddy et al. (1952) does not have this disadvantage, but unfortunately it is less reliable than Norymberski's method (Moxham and Nabarro 1956). The excretion of 17-ketosteroids may be increased, decreased, or normal in Cushing's syndrome, so the level of these steroids is of no value in diagnosis (Butt et al. 1950). Moreover excretion of all steroids is subject to considerable diurnal variation in Cushing's syndrome (Birke et al. 1956); thus the estimation should be made in several (at least three) twenty-four-hour collections of urine.

Anatomical diagnosis is more difficult and should be approached critically. It is of advantage to determine the presence and location of an adrenal tumour, but it is not essential and X-ray methods such as presacral insufflation of air are neither completely reliable nor free of discomfort. We do not think aortography is justifiable; it is

difficult and unreliable in obese patients and may be dangerous. In practice we have relied on straight X-ray examination and tomography, combined with intravenous pyelography to outline the position of the kidney. A large proportion of tumours can be detected by this means.

The final decision about the anatomical lesion is made at operation. In hyperplasia both glands are enlarged (combined weights 10·2–26·1 g. in this series). If a functioning tumour is present the opposite gland undergoes atrophy. The type of lesion can therefore be determined when the first gland is exposed. The appearance of a tumour is obvious on inspection. If the gland is large, but no tumour is present, it can be assumed that hyperplasia is the cause; if it is small it must be left and the opposite side explored.

Preoperative Metabolic Studies

Protein Catabolism

The clinical appearances of the patient are related to factors which may vary independently. Thus severity of muscle wasting depends on duration rather than on the level of negative nitrogen balance. For example, cases 8, 9, and 10 showed only moderate muscle wasting, and this was confirmed by levels of urinary creatinine within normal limits for their known weights before the onset of the disease. Nevertheless, they showed a daily loss of nitrogen between 4·5 and 6·9 g. with a normal protein intake, and in cases 8 and 10 the presence of creatinuria confirmed rapid muscle breakdown. On the other hand, 1 patient (case 1), in whom Cushing's syndrome was due to an adrenal carcinoma, showed gross wasting and the level of creatinine output was roughly half the expected normal; nevertheless at the time of investigation she was losing only 1·4 g. nitrogen daily. In other cases the disease may be rapidly progressive in the absence of muscle wasting and without gross increase in protein catabolism; case 5, a girl aged 18, had florid Cushing's syndrome with severe hypertension, yet the mean daily nitrogen loss was only 0·4 g.

Repletion of protein stores and stimulation of anabolism is extremely difficult in the presence of Cushing's syndrome. The results of high-protein feeding are disappointing, even though the nitrogen balance may become positive at first. Thus in case 1 muscle wasting was severe, and nitrogen equilibrium was achieved on a diet containing 56 g. of protein. When protein intake was increased to 105 g. daily there was a positive balance of 3·1 g. of nitrogen daily from the fourth to the eighth day, but from the fourteenth to the eighteenth day she retained only 0·6 g. nitrogen daily.

We have no data on the effect of high-fat diets in Cushing's disease, but studies were made in a patient with Cushing's syndrome after massive cortisone therapy. A daily intake of 140 g. had no " sparing " effect on protein catabolism, and the daily nitrogen loss was increased by 1·2 g.

Potassium supplements have been shown by Albright (1942) to diminish nitrogen loss in patients with potassium depletion. In 1 patient in this series (case 1), increasing the potassium intake to 200 mEq. daily was followed by a decrease in urinary nitrogen of 1·3 g. daily. In another patient (case 5) a moderate increase of potassium intake from 60 to 90 mEq. daily was sufficient to correct potassium depletion (as indicated by serum level) and urinary nitrogen fell to 0·5 g. daily. These results indicate that high potassium intake diminishes nitrogen loss, but this is incidental to the potassium repletion and is not otherwise of value in countering protein breakdown.

The known action of testosterone in promoting anabolism led Albright et al. (1941) to investigate its value in Cushing's syndrome, and it was found to produce significant nitrogen retention. We have studied the effect of testosterone propionate on 1 patient (case 9) in different states of nitrogen balance. Before operation he was in negative balance of 4·5 g. nitrogen daily. Intramuscular testosterone 25 mg. daily for five days reduced this to 2·06 g., but it was not possible to reverse the negative balance. After adrenalectomy the patient was in positive balance and the same course of testosterone increased this by 2·56 g. daily—i.e., the anabolic effect was quantitatively similar whether the patient was initially in positive or in negative nitrogen balance. The expected potassium retention corresponding to the nitrogen retention during these two periods of testosterone administration should be 6·6 and 6·9 mEq. daily. The observed diminution in urinary potassium during the two periods was 6·6 and 9·3 mEq. respectively, the serum-potassium remaining constant.

TABLE I—PREOPERATIVE METABOLIC DATA

Case no.	Study	Days of collection	Balance (mean daily)		Glucose-tolerance test blood-sugar (mg. per 100 ml.)			Remarks
			N (g.)	K (mEq.)	Fasting	¾ hr.*	2 hr.*	
1	Untreated	4	−1·4	+15		Diabetic		Serum-K 2·3 mEq. per litre
	High K intake	5	−0·1	+80				Serum-K rose to 3·1 mEq. per litre
	High protein:							
	4th–7th day	4	+3·1					
	14th–17th day	4	+0·6					
5	Untreated	6	−0·4	+3	70	146	150	Serum-K 3·6 mEq. per litre
	High K intake	8	+0·11	+20				Serum-K rose to 4·35 mEq. per litre
8	Untreated	5	−6·9	−8	66	128	72	Studied during relapse, serum-K normal
9	Untreated	5	−4·53	+17	90	124	150	
	Testosterone	5	−2·06	+23				
	4th week after adrenalectomy	5	+4·24	+19				Serum-K normal
	Testosterone	5	+6·31	+28				
10	Untreated	4	−5·2	+3	84	130	102	Serum-K normal
14	„	3	+1·5	—	104	200	132	Serum-K normal
16	„	2	+1·7	+2	80	132	132	Serum-K normal
17	High K, high protein diet, and insulin	4	+5	+30		Diabetic		Serum-K 4·7 mEq. per litre. Had risen from 3·1 mEq. after 3 weeks on high-K diet. High-protein diet only for one week

* After 50 g. glucose by mouth.

Impaired sugar tolerance is a characteristic feature of Cushing's syndrome, and its assessment has some value in diagnosis. It is in part related to the degree of increased protein catabolism and in part to the antagonism between hydrocortisone and insulin. In this series abnormal glucose-tolerance curves were obtained in 13 of the 18 patients. (In case 8 the curve was abnormal before his initial operation, but normal during the relapse of Cushing's syndrome two years later.)

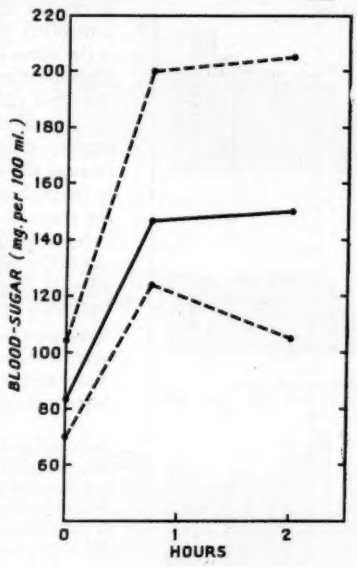

Fig. 1—Glucose tolerance in 10 cases with impaired tolerance: continuous line, mean; interrupted lines, maximum and minimum blood-sugar levels.

3 were typical diabetic curves—1 in the case of adrenal carcinoma (case 1) and 2 in patients with adrenal hyperplasia (cases 3 and 17). The mean curve for the remainder is shown in fig. 1. There was no consistent relationship between the degree of decreased carbohydrate tolerance and negative nitrogen balance—which indicates that antagonism between hydrocortisone and insulin is chiefly accountable for the diabetic behaviour in Cushing's syndrome.

Electrolyte Disturbances

Disturbances in electrolyte balance in Cushing's syndrome were first reported by McQuarrie et al. (1937). Teabeaut et al. (1950) and Sprague et al. (1950) noted hypokalæmia with hypochloræmic alkalosis, usually associated with adrenal carcinoma. Such a finding is rare in Cushing's syndrome, and in this series was observed only once (table II, case 1). In this patient the serum-potassium was 2·3 mEq. per litre, serum-sodium 139 mEq. per litre, serum-chloride 86 mEq. per litre, and serum-bicarbonate 41 mEq. per litre; at operation an adrenal carcinoma was found. Gross muscle weakness was present, and this was abolished when the serum-potassium rose to 3·1 mEq. per litre following high potassium intake. During the phase of severe hypokalæmia the patient was in positive balance, as in the case recorded by Teabeaut et al. (1950). The degree of potassium loss was not related to nitrogen loss, which was only slight. Furthermore, although a positive potassium balance was quickly obtained, complete repletion proved difficult since the urinary output of potassium rose following increased intake. This would be expected if the potassium loss were due to excessive production of mineralocorticoids—not necessarily due to aldosterone, as Garrod and Tait (1957) found no increase in urinary aldosterone in their cases of Cushing's syndrome with hypokalæmia.

TABLE II—PREOPERATIVE SERUM-ELECTROLYTES (MEQ. PER LITRE) (ABNORMAL FIGURES)

Case no.	Sodium	Chloride	Potassium	Bicarbonate
1	139	*86*	*2·3*	*41*
4	*164*	*108*	4·0	30
5	137	105	*3·6*	30
6	140	*109*	*3·3*	30
7	*152*	*112*	4·1	..
9	*150*	101	4·8	31
11	*156*	*95*	5·0	29
12	*163*	*110*	*3·5*	..
17	143	98	*3·1*	32

Abnormal readings in italics.

Lesser degrees of potassium depletion were found in 4 of 15 patients with Cushing's syndrome due to adrenal hyperplasia (table II), and again there was no correlation between the rate of protein catabolism and potassium depletion (table I). The serum-potassium levels were below 4·0 mEq. per litre, but there was no fall in serum-chloride or rise in serum-bicarbonate. Case 5 was in potassium equilibrium when the serum-potassium was 3·6 mEq. Complete and sustained potassium repletion was obtained by increasing the intake by 30 mEq. daily. The cumulative balance over fourteen days showed a retention of 181 mEq. of potassium (the serum level rising from 3·6 to 4·35 mEq. per litre) and 53 mEq. of sodium, and a loss of 137 mEq. of chloride. This indicates a loss of intracellular chloride as cellular potassium is restored. It is apparent that hypochloræmic alkalosis is a late result of potassium deficiency and that in the earlier stages we find only a lowered serum-potassium. Moreover, potassium replenishment is achieved easily when the serum chloride and bicarbonate are normal, but with considerable difficulty at the stage of hypochloræmia. In either case, correction of potassium deficiency is an essential preliminary to operation.

An abnormally high serum-sodium level was found in 5 of the 15 cases, and, of these, chloride was increased in 3 and potassium was decreased in 1 (table II). This hypertonicity of the serum was probably due to sodium retention. Pitting œdema was present in 1 patient, but water retention did not usually balance sodium retention. 1 patient (case 10) was studied over a period of seven days during which there was a loss of 4 lb. in body-weight and 107 mEq. of sodium, yet the serum-sodium rose from 150 to 162 mEq. per litre. Although salt retention, being less severe, has not the practical importance of potassium depletion, this aspect of Cushing's syndrome should not be neglected.

TABLE III—TOTAL NITROGEN LOSS AND TOTAL CREATININE EXCRETION IN SEVEN DAYS AFTER ADRENALECTOMY

Case no.	Creatinine (g.)	Nitrogen (g.)
8b	13·73	50·4
8a	12·23	55·2
10	9·89	88·3
16	7·05	27·26
15	6·16	39·8
14	5·01	28·02
17	4·71	12·8
1	3·77	0

Treatment

Selection of Cases and Operation

We have selected for operation only those patients in whom the diagnosis of Cushing's syndrome was beyond doubt and the disease was definitely progressive. Assessment of rate of progress has been based on clinical features such as hypertension, muscle wasting, and weakness, together with the data obtained from metabolic studies of protein catabolism and electrolyte disturbances.

Previous work (Sprague et al. 1950) showed that at least 75% of hyperplastic adrenal tissue must be removed in order to reverse the metabolic disorder in Cushing's

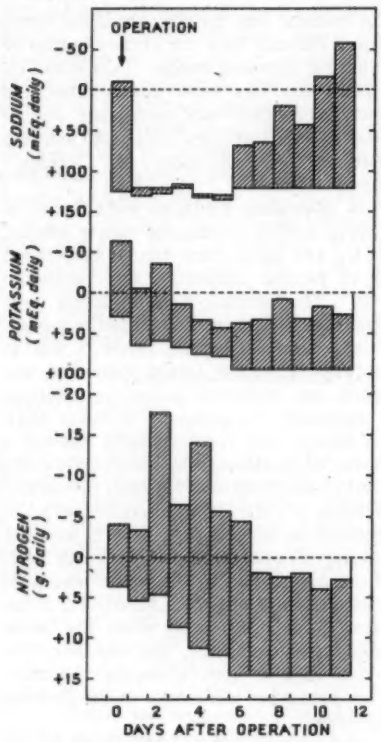

Fig. 2—Balance data, case 8a.

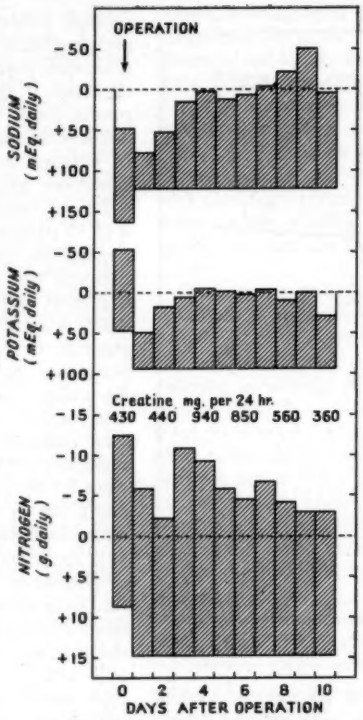

Fig. 3—Balance data, case 8b.

to normal levels is gradual and controlled. The dosage scheme is the same for total or subtotal adrenalectomy in a single operation, but differs when the procedure is carried out in two stages. In the single-stage operation the dosage of cortisone is far higher than that required for removal of normal adrenals (Mason 1955) and varies according to the degree of preoperative adrenal hyperfunction. The following dosage schedule has been found suitable for a one-stage adrenalectomy in patients with active progressive Cushing's syndrome:

	mg. daily
For two days before operation	150
Day of operation and subsequent two days	300
Fourth and fifth day after operation	200
Sixth day after operation ..	150
Seventh day after operation..	100

Cortisone then to be given orally (four doses per day) and reduced every other day to maintenance levels (25–50 mg. daily).

Cortisone was not given orally over the immediate period of the operation, because of the syndrome. There is, however, a very narrow margin between removing enough adrenal tissue to prevent relapse and so much that adrenal hypofunction results. In patients under 25 years, and in rapidly progressive, very severe Cushing's syndrome at any age, there is for practical purposes no margin and total adrenalectomy is the operation of choice (Mason 1957). In patients over 45 years, with a more slowly progressive disease, relapse is less likely and subtotal adrenalectomy, leaving only 20–25% of the adrenal tissue, is both adequate and safer.

These patients are more likely to suffer from hypertensive vascular disease, which is unlikely to be relieved by the operation and adds to the surgical risk. Removal of the adrenals by two operations is often advocated (Bishop et al. 1954, Montgomery and Welbourn 1957), and we would endorse this view as regards older patients—especially those with evidence of hypertensive vascular disease. In younger patients, however, we feel that, with adequate preparation, the immediate surgical risks of bilateral adrenalectomy in a single operation are less than in two operations, largely owing to the greater hazard of postoperative chest complications associated with two operations.

Preoperative Medication

This is needed, first, to correct the existing metabolic disturbance and, second, to cover the sudden deprivation of cortical steroids by adrenalectomy. In the rare cases with a diabetic sugar-tolerance curve, insulin will be required. The main preoperative therapy is, however, adequate cortisone administration. This must be sufficient to maintain the excessive level of circulating glucocorticoids to which the patient has become accustomed, and after operation the dose must be adjusted so that reduction

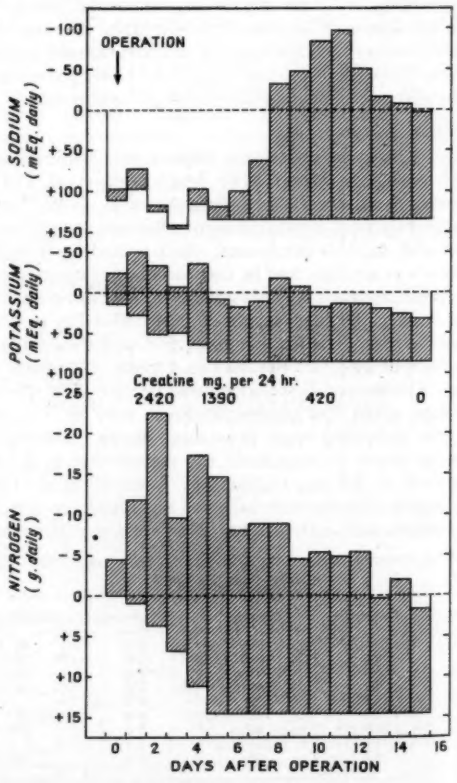

Fig. 4—Balance data, case 10.

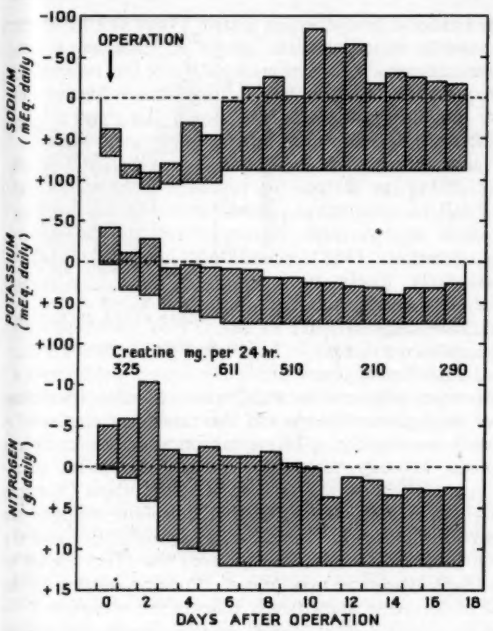

Fig. 5—Balance data, case 14.

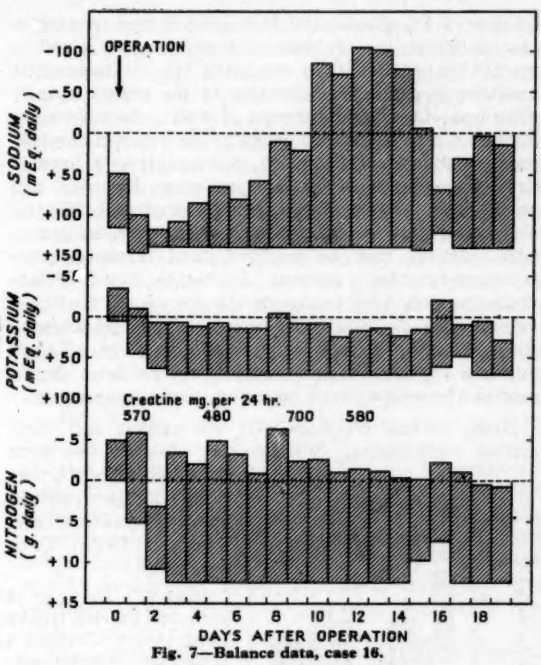

Fig. 7—Balance data, case 16.

dangers of vomiting and defective absorption. Intramuscular injections were given twice daily, starting at least forty-eight hours before operation to ensure adequate absorption. Postoperatively the injections were replaced by oral cortisone only when gastrointestinal function had returned to normal.

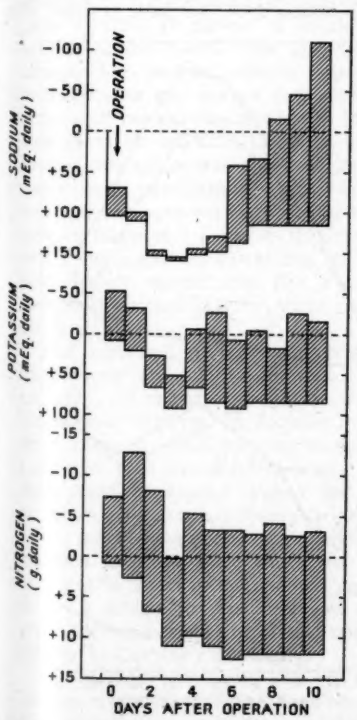

Fig. 6—Balance data, case 15.

No evidence of postoperative adrenal insufficiency has appeared in patients treated with the above regime. Substitution therapy with cortisone alone is sufficient, and the balance data recorded below confirm that there is no need for addition of a mineralocorticoid such as deoxycortone acetate or fluorohydrocortisone in the early postoperative phase.

Operative Details

Whether total or subtotal adrenalectomy is to be performed the right adrenal is first removed complete. The subcutaneous tissues and muscles are infiltrated with 120 ml. of 0·3% lignocaine with 0·5 ml. 1 in 1000 adrenaline on each side. If the hypertension is severe the adrenaline is omitted. The 11th rib is resected, the diaphragm is divided, and the peritoneum is freely opened. The kidney is pushed down and the lung upwards. On the right side the liver must be pushed up, and on the left the spleen and pancreas displaced medially after division of the peritoneum between spleen and diaphragm. On the right the inferior vena cava is located, and then the medial border of the adrenal gland; the wide short vein thus exposed between the two is divided. Sometimes the adrenal is wrapped round and extends behind the vena cava; this part must be dissected, and then the rest from medial to lateral. In this way the most difficult part of the dissection is done in a dry field. The wound is closed in layers without drainage.

If subtotal adrenalectomy is to be done the whole of the left adrenal is displayed after removing the right. An incision is made at a level which would leave $^1/_8$–$^1/_{10}$ of the gland, according to its size. If the medial cut surface bleeds and retains its normal colour, its blood-supply is presumed to be adequate and the lateral portion is removed. Biopsy specimens are taken from both kidneys to assess the extent of renal vascular damage.

When the patient is turned after the first side is completed, shock may develop even though blood loss has been slight. This is due to loss of vasomotor tone in the anæsthetised patient, leading to pooling of blood on the dependent side. A blood-transfusion must therefore be started at the end of the operation on the first side.

Subtotal resection of each adrenal is in our view inadvisable since, if relapse occurs it is impossible to decide which side should be re-explored. Complete removal of the right adrenal is preferable since hypertrophy of a remnant is more difficult to deal with on this side owing to proximity to the vena cava.

Postoperative Care and Complications

On return from the theatre the patient is nursed with blocks to the foot of the bed. These are removed when consciousness returns. Over the next twelve hours the patient is gradually raised, according to the level of the blood-pressure, to a sitting position. An intravenous

infusion of 4% glucose and N/5 saline is kept running in case noradrenaline or hydrocortisone is needed, and to provide the necessary fluid and electrolytes. Intramuscular cortisone is continued according to the regime already described. Oral administration of water, electrolytes, or hormones is to be avoided owing to the common development of abdominal distension, presumably as a form of ileus, due partly to the retroperitoneal dissection and partly to the pre-existing metabolic disturbance. Gastric aspiration, intravenous fluids, and electrolytes, analgesics, and sedatives may be required until normal gastrointestinal function is restored. During the first few postoperative days fluid intake should not exceed the urine volume plus 1·5–2·0 litres for insensible loss, and not more than 140 mEq. sodium daily should be given. Larger amounts are harmful and may prolong the ileus. Intravenous administration of potassium seems unnecessary.

Acute adrenal insufficiency is the earliest and most serious complication. We have not observed this since the adoption of the cortisone dosage described above. Before this, however, 1 fatal case occurred.

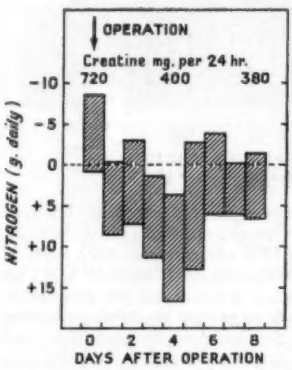

Fig. 8—Balance data, case 17.

Case 6, a girl aged 16 years, had a severe, rapidly progressive Cushing's syndrome. Bilateral subtotal resection of the adrenals was carried out leaving approximately 1/10 of each gland. There was no incident in her progress until eleven hours after her return to the ward, when she collapsed with a rapidly rising pulse-rate and, rather later, a severe fall in blood-pressure. Electrocardiography revealed sinus tachycardia with no evidence of electrolyte imbalance. The pulse-rate remained at 160, and the blood-pressure was unrecordable. The extremities were extremely cold and pale; there was no respiratory difficulty and no abnormal signs were found in the chest. She was mentally alert and very apprehensive, and complained of weakness; vomiting and nausea were absent. Her condition remained virtually unchanged until death twenty-eight hours after operation. Necropsy revealed bilateral thrombosis of the adrenal remnants but gave no definite indication of the cause of death. In this case 75 mg. cortisone had been administered intramuscularly daily for two days, and a further 150 mg. was injected three hours before adrenalectomy. After operation a further dose of 150 mg. was injected soon after she collapsed. The total water intake, mainly intravenous, was 5 litres in the twenty-four hours after operation; the urine volume over this period was 1 litre. Intravenous noradrenaline was given in an attempt to raise the blood-pressure, but despite continued and increasing dosage had no significant effect.

Subsequent experience and the reports of other observers clearly indicate that this syndrome is due to inadequate cortisone therapy before and immediately after operation. A possible contributory factor was the excessive water intake. The failure of noradrenaline to raise the blood-pressure in these circumstances has been noted by others, and the correct emergency treatment is now known to be continuous intravenous administration of hydrocortisone hemisuccinate 50 mg. initially followed by 10 mg. per hour. This is a most effective treatment for acute adrenal insufficiency, and should always be immediately available for patients undergoing adrenalectomy.

In addition to this acute form of cortical insufficiency, symptoms may arise more insidiously owing to a too rapid fall in circulating corticoids at any time after operation. This is particularly likely to occur after radical subtotal adrenalectomy, if the adrenal remnant produces insufficient hormone when cortisone is withdrawn. Similar symptoms occur during convalescence if the dosage of cortisone is lowered too rapidly. The symptoms include complete anorexia, lethargy, arthralgia, mental depression, irritability, and withdrawal from contact with others (Sprague 1953, Cope and Raker 1955). Electrolyte changes are absent, the pulse-rate seldom rises significantly, and the blood-pressure is maintained; indeed the hypertension of Cushing's syndrome may persist. Prompt increase in the dose of cortisone immediately relieves the symptoms.

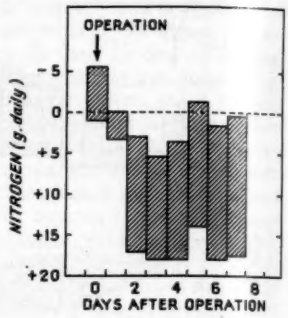

Fig. 9—Balance data, case 1.

Pulmonary complications are next in severity. It is most important at the end of the operation to expand the lungs fully to minimise this risk. Hæmothorax and pneumothorax occurred in 2 patients, but responded to appropriate treatment, with complete re-expansion of the lung. In 1 patient infection developed in the left subphrenic space; this drained spontaneously and the sinus took a considerable time to heal. There is a definite risk of fatal pulmonary emboli (Mason 1957) in those patients who

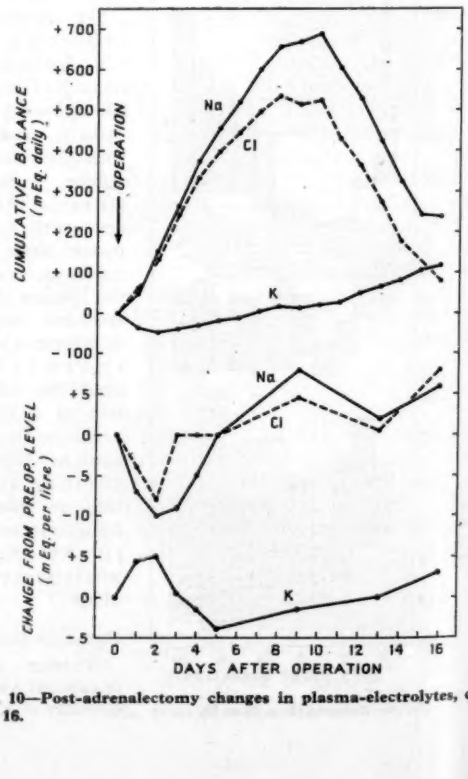

Fig. 10—Post-adrenalectomy changes in plasma-electrolytes, case 16.

are weak and heavy, with a sluggish peripheral circulation and a tendency to bruise easily. Owing to abdominal distension and a liability to postural hypotension adequate postoperative movement is difficult to achieve. 3 patients in this series had a non-fatal pulmonary embolus.

In 1 patient (case 13) the hæmoglobin fell steadily by about 10% each day for five days. After blood-transfusion her hæmoglobin rose and did not fall again. There was no clinical evidence of bleeding in the pleural or peritoneal cavities or of gastrointestinal hæmorrhage, and chest X-ray showed no abnormality. This phenomenon was never explained.

In this series of 17 cases there have been 2 deaths; the 1st (described above) due to acute adrenal insufficiency and the 2nd, in a patient aged 54, due to a combination of hypertensive heart-failure and respiratory failure associated with postoperative pulmonary collapse (case 17). This 2nd case illustrated the operative risk in an elderly patient with poor respiratory and cardiac reserve.

Postoperative Metabolic Studies

Information on the metabolic changes after bilateral adrenalectomy in Cushing's syndrome is scanty. As this has a considerable bearing on treatment, postoperative balance studies were made on 7 patients in this series. (Case 8 was studied twice: (a) at initial operation; (b) at second operation on account of relapse after eighteen months.) The results are illustrated graphically in figs. 2–9. The direction and duration of changes in nitrogen, potassium, and sodium balance are similar to those found after any form of operation or trauma (Moore and Ball 1952). In 3 instances (cases 8a and b and 10) nitrogen loss was heavy, and in all it was maximal at the first to third day after operation; positive nitrogen balance was usually achieved by the seventh to twelfth day. Another patient (case 9, table I) showed a strongly positive nitrogen balance several weeks after operation. The degree of nitrogen loss was not directly related to the dosage of cortisone, but was greater than that observed after the removal of normal adrenals (A. S. Mason, unpublished). This is to be expected since the preoperative level of protein catabolism was raised in these patients. There was a rough parallelism between the degree of nitrogen loss and the postoperative output of creatinine, which may be taken as a guide to the lean body mass. Thus case 1 (with adrenal carcinoma) and case 17, who were both grossly wasted and had a subnormal creatinine excretion, showed a very slight postoperative loss of nitrogen.

This increased protein catabolism after operation is qualitatively the same as normal protein breakdown—i.e., 90% of urinary nitrogen is in the form of urea. There was, however, an increase in urinary creatine in the 5 cases in which this was measured after operation compared with preoperative levels. Case 10, with the most negative nitrogen balance, had the highest creatine excretion over a twenty-four-hour period (2·42 g., fig. 4), and in others creatinuria was proportional to the degree of nitrogen loss (see table III). This finding presumably indicates a rapid postoperative breakdown of muscle tissue; a similar but smaller degree of creatinuria occurs after other operations—i.e., this is not specific for adrenalectomy in Cushing's syndrome.

Postoperative potassium loss was slight and a positive balance was achieved after the first three days. Serum-potassium levels remained normal throughout, but usually rose slightly in the first three days after operation. Changes in sodium and chloride were greater; retention of these persisted until the seventh to the tenth day after operation, when diuresis occurred. During the first forty-eight to seventy-two hours after operation water was retained in excess of sodium; the consequent fall in serum-sodium level was from 6 to 9 mEq. per litre in 7 cases. A typical curve is shown in fig. 10. Nevertheless all these patients were in positive sodium balance. Thus case 15 retained 70 mEq. of sodium in the first twenty-four hours after operation, but the serum level dropped by 6 mEq. per litre. Case 10 retained 431 mEq. of sodium in the first four days after operation, and the serum level fell by 9 mEq. per litre. Sodium retention continued for some days after water excretion returned to normal, so the serum concentration was restored to preoperative levels or above by the fifth or sixth day after operation. Certain practical conclusions can be drawn from these results. Firstly, measurement of serum levels gives no accurate indication of electrolyte balance. Secondly, there is no need to administer additional mineralocorticoids (such as deoxycortone) over the immediate period of operation. Thirdly, the daily intake of sodium, either intravenously or by mouth, should not exceed 140 mEq. daily. Lastly, the amount of water given intravenously and by mouth during the first two to three days after operation should not exceed the urine volume by more than 1–1·5 litres daily.

These observations apply only to the initial phase of sodium and water retention. In the later period of convalescence the patient requires a high salt intake if electrolyte balance is to be maintained with cortisone therapy. Some patients will undoubtedly require not only cortisone but the continued administration of a mineralocorticoid; fluorohydrocortisone is the most suitable hormone for oral therapy.

Summary

Preoperative and postoperative studies have been made in 17 patients with Cushing's syndrome associated with bilateral adrenal hyperplasia, and in 1 case of adrenal carcinoma. The following conclusions have been reached:

(1) The diagnosis and the progressiveness of the disease must be established beyond doubt before surgery is undertaken.

(2) Both the disturbance of physiology and the anatomical lesion must be considered. There are at present no adequate methods of restoring protein. The electrolyte disturbance must be corrected before operation.

(3) In the younger patients and in those with rapidly progressive disease total adrenalectomy is recommended. In older patients subtotal adrenalectomy is preferred. In the younger patients the operation is carried out in one stage and in older patients in two stages.

(4) The most important item in the immediate preparation for surgery is administration of sufficient cortisone to maintain the excessive level of glucocorticoids to which the patient has become accustomed. To ensure absorption over the time of operation and during the postoperative period the cortisone must be given intramuscularly. Intake of water and sodium must be limited in the immediate postoperative period. The dose of cortisone must be gradually reduced, and later the amount of salt increased.

(5) The most serious postoperative complication is acute adrenal failure. It should be treated by hydrocortisone hemisuccinate, which should always be available in case of emergency. The other complications are ileus, pulmonary embolism, hæmothorax, and pneumothorax.

We are grateful to the physicians of the hospital who have sent us patients, and especially to Prof. Clifford Wilson who has also given us advice in the preparation of this paper; to Mrs. Scott, sister in

charge of the metabolic wards, who did so much to help us with these studies; and to Mr. G. C. Tresidder who operated on one of the cases and has permitted us to refer to this patient.

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MALIGNANT DISEASE OF THE URINARY TRACT *

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MALIGNANT growths of the kidney and ureter account for only about 2% of all malignant tumours; yet their clinical presentation is so variable that they often present a difficult diagnostic problem. Nevertheless this problem can be solved with almost complete certainty if the right investigations are done. These growths show in a striking manner that duplicity which we have come to associate with cancer of the urinary tract: whilst some are highly lethal, others follow a relatively benign course. The outcome in an individual patient, however, can be foretold with some confidence when all the facts are known.

THE KIDNEY

In a nation-wide survey of over 2000 cases collected for the British Association of Urological Surgeons in 1951 parenchymal tumours accounted for about 75% and tumours of the pelvis for about 12% of renal cancers. The remainder included some of the most interesting rarities of surgical practice, as well as the Wilms tumours in children. My personal series includes 142 cases (table I). The adult parenchymal tumours are solid

TABLE I—MALIGNANT DISEASE OF THE KIDNEY

Parenchymal carcinoma	89
Secondary carcinoma	1
Sarcoma	1
Pelvic tumour { Epithelial	43
Pelvic tumour { Sarcoma	1
Tuberous sclerosis	1
Wilms tumours	6
Total	142

adenocarcinomas arising in renal epithelial cells: they are better known as Grawitz tumours, or by the now discredited name of hypernephromata. The pelvic tumours can be either papillary, like similar tumours in the bladder, or solid and either transitional- or squamous-cell.

* Based on the third Lettsomian lecture for 1958, delivered before the Medical Society of London.

Pathology

Whilst there is no proof that a benign renal adenoma can become malignant, there is considerable probability that it does so (Newcomb 1937, Thackray 1953). The possibility of a hormonal factor in the ætiology is suggested by the 2-to-1 preponderance of males over females; chronic simple infection and stone-formation appear to have an influence on the production of the uncommon squamous cell carcinoma of the renal pelvis. Papillary tumours of the pelvis may also result from the excretion of carcinogens; but, unless there is unilateral hydronephrosis, this explanation hardly accounts for their usual one-sided distribution.

Renal tumours can spread by direct extension and by the lymphatics; but they endanger life chiefly by their predilection for invading venous radicles, the renal vein, and the inferior vena cava.

The particular tendency of papillary tumours of the pelvis is to spread to other parts of the urinary tract by the urogenous dissemination either of cells or of a carcinogenic agent.

Clinical Features

In a disease with such wide pathological variations it is to be expected that the clinical manifestations will also differ from patient to patient. It becomes all the more important to pick out the cardinal symptoms and signs. In renal neoplasms there is a classical triad—hæmaturia, pain, and tumour. These may be late in appearance, and they may not all be present in any one case; but in most patients they give the first evidence of the disease.

Intermittent fever occurs in some cases of both parenchymal and pelvic growth (Griffiths and Thackray 1949, Rowlands 1951). Without necrosis it may be an anaphylactic manifestation (Wright 1922); but, whatever its cause, in my experience it indicates a bad prognosis. Loss of weight and anæmia may occur, as in any malignant condition. Varicocele on the right side should still be regarded with suspicion, despite the rarity of one which disappears after right nephrectomy.

The primary lesion in the kidney may not declare itself until it erodes a calyx or until it attains a large size. Before this it has sometimes invaded a vein; and it may have given rise to distant metastases or, quite often, to a solitary deposit.

Of skeletal sites the spine heads the list, and sudden paraplegia may be the first indication of renal neoplasm. A deposit in a long bone may appear as a pulsating swelling, with the radiographic picture of bone destruction; it can be a teasing examination problem. In the lungs the metastases are generally multiple, but solitary tumours have been excised: and palpable enlarged lymph-nodes in the neck are sometimes found at an early stage.

In at least 4 known cases priapism from a deposit in the penis was the presenting symptom. There is, in fact, scarcely a part of the body, including the skin, the thyroid, and the testis, in which a metastasis has not been the first indication of a renal tumour; and because such secondary tumours are so often solitary, their excision may be the proper procedure.

The incidence of such a presentation was given as 50% by Israel in 1896 and as 9% by Deuticke in 1931; but in our series in 1951 it was only 3·2%. Such is the effect of modern methods of investigation.

The true silent tumours are those which are discovered at necropsy, or when operating for some other condition, such as stone. I have seven of these on record.

Diagnosis

The aim of diagnosis is not limited to the finding of an neoplasm in the kidney. It should disclose whether the growth is parenchymal or pelvic, because the treatment of the two differs; and it should determine its operability and the presence of complications. It may also give some idea of the prognosis.

An opportunity to perform cystoscopy whilst bleeding continues should be seized gratefully. If blood is seen coming only from one ureteric orifice the site of bleeding is at once determined. The decoy prostate is eliminated, and that refuge of the destitute, varicose veins in the bladder, is no longer needed.

Excretion pyelography is always very informative and, if there has been no opportunity for cystoscopy during bleeding it should be the first major investigation. Retrograde pyelography is essential if there is no excretion or poor definition on the intravenous pyelogram. In any event it will give a good idea of the extent of the filling defect; and it should serve to distinguish a parenchymal from a pelvic growth.

Aortography

Despite the clear picture it gives, a retrograde pyelogram shows only that there is a space-filling lesion. In practice this may be a tumour or a cyst; and, although the diagnosis can often be inferred from the clinical features, the distinction can generally be made by aortography—which is not such a terrible investigation as some seem to think.

A parenchymal tumour is vascular: the vessels are displaced, and there is usually an irregular deposit of contrast medium in the venous spaces of the growth which gives it a mottled appearance. This is known as " pooling ". By contrast, a cyst is avascular: it shows as a clear area in the nephrogram. Pelvic papillary tumours show no specific signs on aortography. Solid pelvic tumours are avascular; a pelvic tumour which invades the parenchyma may give rise to an avascular defect in the nephrogram, as may a parenchymal tumour which invades the pelvis.

Perhaps the greatest value of aortography will prove to be in the detection of an early carcinoma when the pyelogram is equivocal or the ureter cannot be catheterised. We have thus diagnosed a tumour only 15 mm. in diameter.

Perirenal Oxygen Insufflation

Although rarely needed in the diagnosis of renal tumours, the injection of oxygen by the presacral route can show whether the growth is fixed to its surroundings. This may determine the degree of operability and the need for preoperative irradiation.

Treatment and Prognosis

There is general agreement, at least among surgeons, that the treatment of carcinoma of the kidney is nephrectomy with early ligation of the renal vein and removal of the perinephric fat. It is also accepted that in papillary tumours of the pelvis the ureter should be removed with the kidney. There is some difference of opinion on the value and place of irradiation in treating kidney cancer. A study of the survival-rates has a bearing on these matters (Priestley 1939, Griffiths and Thackray 1949, Riches, Griffiths, and Thackray 1951): it shows that, whilst some of these growths are rapidly fatal, others progress slowly. We have tried to analyse the various factors which influence the prognosis in the individual case.

1. Histological Grade

The grading is similar to that described for bladder tumours: it is based solely on the microscopic appearance. The objection has been raised that areas of different grades may be found in the same growth; but just as one bad link weakens a chain, so one area of high malignancy condemns the whole tumour.

Of 80 tumours removed by nephrectomy 39 were grade-1, 25 were grade-2, and 16 were grade-3. There were 6 operative deaths. 8 further cases were deemed inoperable; and in a fit lady of eighty-seven, with a three-year history of hæmaturia suggestive of a slowly growing tumour, I decided not to operate.

TABLE II—5-YEAR SURVIVAL OF PATIENTS OPERATED ON BEFORE JANUARY, 1953

—	Number of cases	Survivals
Total	59	29 (49%)
Grade 1	27	18 (67%)
Grade 2	19	8 (42%)
Grade 3	13	3 (23%)

Table II shows that a rising scale of histological malignancy is reflected in a lower survival-rate. A similar conclusion was reached in 100 patients in the B.A.U.S. series; and Thackray (1957) has shown more recently the same correlation in patients followed for ten years.

2. Involvement of the Renal Vein

Macroscopic invasion of the renal vein was seen in 13% of low-grade and 44% of high-grade tumours in this series. It can generally be recognised at the time of operation; and an attempt should be made to tie the vein beyond the malignant thrombus. It reduces the five-year survival for all grades from 49 to 28%.

3. Invasion of the Lymph-nodes

Invasion of lymph-nodes occurred in 6 patients in equal proportions in the three grades: 2 lived for about seven years, 1 for four, and 1 for three years. Although survival is shortened, these glands respond well to postoperative irradiation. If possible, they should be removed with the kidney. Excision of recurrent invaded glands in the neck is also worth while. Ultimately 5 of the 6 cases developed other metastases.

4. Local Extension

Local infiltration of the perinephric fat, muscles, the colon, the pancreas, or other viscera had taken place in 23% of my cases. It was more frequent in growths of high-grade malignancy. Its effect on survival is serious, but it does sometimes respond to irradiation.

5. The Presence of Metastases

The existence of metastases is not always a contra-indication to nephrectomy. This may be required for the relief of pain, hæmaturia, or pyrexia, or on the assumption that removal of the primary growth is likely to make irradiation of the secondary more effective.

Metastases were present at the time of the nephrectomy in 9% of my patients. Separate excision of a metastasis from the chest wall was possible in 1 patient only; but he is alive nearly five years later. Others have had relief from X-ray therapy. My figures are insufficient to show whether metastases are commoner with high-grade growth; but I believe that they are. It is certain that grade-3 metastases grow more quickly and destroy life earlier.

6. The Method of Treatment

So long as the surgical treatment is radical enough, any approach which gives a wide exposure may be adopted.

I prefer generally to work through the bed of the excised twelfth or eleventh rib; conversion to the Nagamatsu incision is possible if required. I do not find it easier to secure the renal vein earlier by the abdominal route: this is so by the abdominothoracic exposure, but a kidney which can only be removed in this way may not be worth removal. In the

B.A.U.S. series there was a higher operative mortality after the abdominal than after the lumbar incision.

The use of X-ray therapy is controversial. There is no doubt that some renal carcinomas are radiosensitive; and there is enough evidence to show that the more anaplastic ones are the more responsive. In the larger series (1951) the addition of postoperative conventional X-ray therapy improved the results in all cases; but survival figures were improved most in those, largely of high-grade malignancy, in which the vein was involved. Since then I have made it the rule to advise postoperative X-ray therapy for most patients, excluding only those with small tumours of low malignancy, very fat patients, and those who cannot take it. The certain indications for it are tumours of high malignancy, venous involvement, lymph-node invasion, or local extension.

In a small but increasing number of patients preoperative X-ray treatment has also been given; and study of such patients, known to me personally, has been instructive. Some, who would be expected to do badly, have done well.

A woman of forty-nine had a tumour which appeared both clinically and on perirenal oxygen insufflation to be fixed. After X-ray treatment it became smaller and more mobile, and the oxygen passed around its upper pole. The kidney was removed without difficulty: though it was a grade-2 growth and the vein was invaded she is alive and well six and a half years later.

A man of forty-seven was found at operation elsewhere to have a fixed, irremovable kidney: the wound was closed and he was given X-ray therapy. I then exposed the kidney again, divided some dense scar tissue, and removed it. This was also a grade-2 growth with the vein invaded, but he is alive and well eleven years later.

A man of fifty-five had hæmoptysis. A shadow near the sixth rib posteriorly was suspected as a carcinoma of the bronchus; but investigations at a chest hospital proved negative. A year later he had hæmaturia, and we found a right renal tumour. The thoracic shadow was now clearly a destructive palpable metastasis in the ribs. He was given conventional X-ray therapy to the rib area and treatment on the linear accelerator to the kidney. I then did a nephrectomy. The kidney was adherent and on section necrotic; but it was a low-grade tumour with the vein free. The lesion in the ribs has shown a progressive diminution in size and apparent calcification in its outline; it is no longer palpable and he is very well at the end of a year.

In view of such cases I feel that more use should be made of preoperative radiotherapy, especially if supervoltage machines are available. The diagnosis must be certain and aortography may be necessary to make it so. If the histological grade or the state of the vein could be known before operation the choice would be easier, but I do not think that renal biopsy is justified for this purpose.

I have no doubt that the histological grade of the tumour is the most important single factor in prognosis. High-grade malignancy is beyond our control: but it may prove possible to mitigate its effects by supervoltage therapy. This is our present plan. There are of course exceptions to every rule; in this series they are 3 survivors of fifteen years, thirteen years, and eight years, all with anaplastic tumours. None had irradiation. The vital factor of individual resistance will always have the last word in the argument.

RENAL PELVIS AND URETER

The widespread involvement of the urinary tract by papillary tumours is shown by the distribution of the 43 cases in this series (table III).

TABLE III—SPREAD OF 43 EPITHELIAL TUMOURS OF THE RENAL PELVIS AND URETER

Distribution	No.
Pelvis alone	15
Ureter alone	4
Pelvis and bladder	9
Ureter and bladder	3
Pelvis and ureter	3
Pelvis, ureter, and bladder	9

These tumours are composed of transitional or squamous epithelium with a few mixed forms. Clinically the important division is into the papillary and the less common solid type: their behaviour resembles that of the papillary and solid growths of the bladder respectively. The squamous-cell tumours are all solid.

6 papillary transitional-cell tumours which were histologically benign are included in the series. 2 of them affected more than one part of the urinary tract: though benign tumours show a higher survival-rate than those described as transitional-cell carcinomas, they have the same age-incidence and the same tendency to spread.

Treatment

The treatment of pelvic papillary tumours is nephroureterectomy. Dealing with the intramural part of the ureter some patients have had a disc of bladder excised; and some, following the advice of Macalpine (1947), have had this part treated by cystoscopic diathermy after section of the ureter flush with the bladder. Coexisting or recurrent growths in the bladder have been controlled by cystodiathermy; but 2 patients needed total cystectomy and ureterectomy after the kidney had been removed elsewhere. I believe that the kidney tumour usually precedes those in the bladder, and recognition of the renal origin of these bladder growths is essential. On the other hand, they may appear in a bladder previously clear as long as two years after nephrectomy and ureterectomy: and failure to remove the ureter may result in tumour appearance in the stump. What is perhaps most important in the removal of these growths is the avoidance of spill, either of urine or of tumour-cells.

A few of the pelvic tumours are radiosensitive. In one man with a fixed, inoperable anaplastic growth the mass became smaller, the affected kidney regained some function, and subsequent inguinal metastases disappeared with radiotherapy. He died after two years from pulmonary metastases.

Dr. Thackray classifies pelvic papillary tumours into low and high grades.

The 10 patients who lived for five years all had tumours of low-grade malignancy. Some have not been available for grading; but out of 18 known low-grade tumours 10 (55%) lived for five years and 4 died earlier from other causes. 7 had recurrence or metastasis. Of 5 patients with known high-grade growths 1 lived for three years and 1 for two; but none of the others passed the six-month mark. 4 of the 5 had recurrence or metastases.

Although a widespread distribution of these papillary growths affects survival adversely, it is not so important a factor as the grade of malignancy. Low-grade tumours gave rise to metastases in the lungs or liver only after long survival, although local recurrence was more frequent. In high-grade tumours bloodborne metastasis was more frequent than local recurrence. The solid transitional-cell tumours are much more malignant: no patient lived for a year after operation; and metastases in the lungs, brain, skin, or lymph-nodes appeared in 5 out of 7. Radiotherapy did not seem to help them.

Squamous-cell growths were too few to analyse, but they are known to have a poor prognosis.

WILMS TUMOUR (NEPHROBLASTOMA)

That infants and young children can be afflicted by malignant disease of the kidney is one of the cruelties of Nature. That it should be of such intense malignancy as is found in Wilms tumour is a refinement of cruelty.

In the B.A.U.S. series (1951) there were 189 cases of nephroblastoma of which half had occurred between the ages of two and four years. Only 8 had been in children under one year, an important fact since it has been shown that the prognosis is better in younger children. Boys and girls are affected equally. Hæmaturia, which indicates extension to the pelvis, is of bad prognostic import; it occurred in 18% of the patients. The renal vein was involved in 8%.

Many of these tumours shrink under the influence of radiotherapy, but Higgins and his colleagues (1951) think that these are of higher malignancy and always recur. Preoperative irradiation has a debilitating effect; and the best reason for its use is to make a very large tumour smaller and easier to remove. Gross (1953) used it in alternate cases for a year; but he found that the mortality " skyrocketed ".

Early nephrectomy without unnecessary manipulation is indicated. It should be followed by postoperative irradiation, starting as soon as possible after operation.

Many observers think that survival of eighteen months to two years implies cure; but metastases have been found as late as five years after nephrectomy and local recurrence after eight years. In the 189 cases we collected the three-year survival was 26%.

The most informative figures are those of the Boston workers (Gross and Neuhauser 1950). They are given in table IV.

TABLE IV—" CURE " RATE OF CASES WITH WILMS TUMOUR (GROSS AND NEUHAUSER)

—		Patients under 1 yr.	Patients over 1 yr.	All ages
Period A	1914–30	42·8%	5%	14·9%
	27 cases (4 cures)			
Period B	1931–39	71·4%	20·8%	32·2%
	31 cases (10 cures)			
Period C	1940–47	80%	43·3%	47·3%
	38 cases (18 cures)			

In period A nephrectomy alone was used.
In period B the transperitoneal route was the rule, but anæsthesia and preoperative and postoperative care had improved greatly.
In period C postoperative X-ray treatment was added.
The term " cure " indicates a two-year survival free from recurrence.

In a few cases, 3·6% according to Scott (1956), the condition is bilateral.

CONCLUSIONS

I hope it is evident that throughout the urinary tract there are two main types of malignant disease. Results of treatment cannot be compared without saying whether the tumours were solid or papillary, and whether they were anaplastic or differentiated. There will also be some which were intermediate.

Though this general survey is based on personal experience, it must be obvious that I owe a great debt to my teams of assistants throughout the years. My colleagues have collaborated generously, and I owe especial thanks to Prof. B. W. Windeyer, to Dr. A. C. Thackray, and to Dr. C. G. Whiteside. Mr. Cowan, the records officer, has checked my figures and made the tables. I must finally express my deep gratitude to my former chief, Sir Gordon Gordon-Taylor, for stimulating my interest in the surgery of malignant disease.

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INTRA-ARTICULAR THERAPY IN RHEUMATOID ARTHRITIS

COMPARISON OF HYDROCORTISONE TERTIARY BUTYL ACETATE AND HYDROCORTISONE ACETATE

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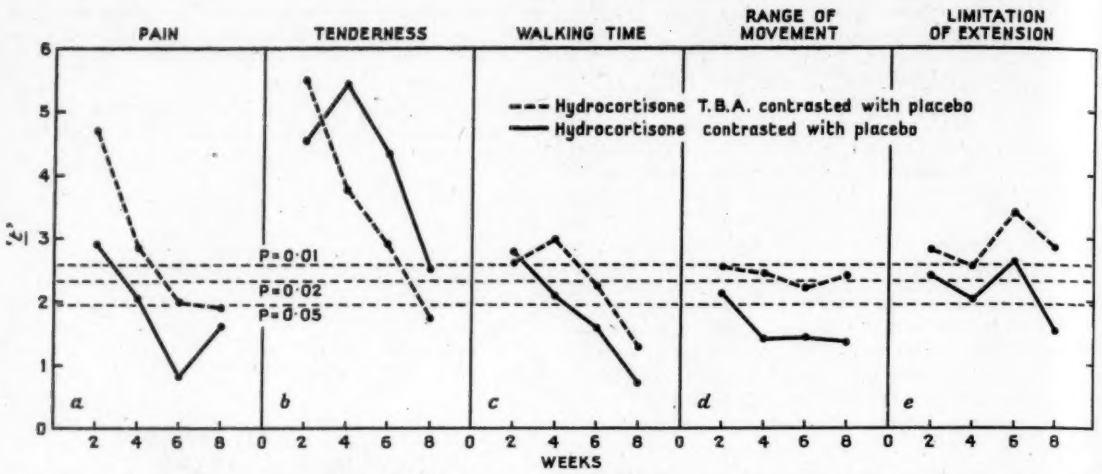
THE intra-articular injection of hydrocortisone acetate, introduced by Hollander et al. (1951), is generally regarded as of value in the treatment of rheumatoid arthritis. Most patients derive subjective benefit but the effect is usually transient. In 1955 a less soluble ester, hydrocortisone tertiary butyl acetate (T.B.A.), was developed for intra-articular therapy with the claim that its anti-inflammatory effects were more pronounced and of longer duration. Hollander et al. (1955) found that of 92 patients with rheumatoid arthritis, 62 experienced greater relief and 49 longer benefit from hydrocortisone T.B.A. than from hydrocortisone. Duff (1956) stated that of the different chemical forms of local hydrocortisone the T.B.A. preparation was probably the most effective. Contradictory results were reported by Zuckner et al. (1956), who found no difference in antirheumatic response between the two compounds. None of these studies were made in strictly controlled conditions. We report here the results obtained by a double-blind crossover trial designed to evaluate these drugs. Each patient received both compounds as well as placebo and thus served as his own control.

Design of Trial

The clinical material comprised 24 patients with rheumatoid arthritis whose principal disability arose from involvement of the knees. In 13 both knees were treated, giving a total of 37 joints suitable for trial on the evidence of active inflammatory changes. No patient was accepted whose treatment within the previous two months had included systemic or intra-articular steroid therapy; symptomatic treatment remained constant throughout the period of study which was conducted under outpatient conditions.



Comparison of effects of hydrocortisone T.B.A. and hydrocortisone. Horizontal axis shows four two-week periods after each course of treatment. Vertical axis shows significance of difference between means of each measurement (t).

***a*, Effect on pain. Significant improvement lasted four weeks after hydrocortisone T.B.A. and two weeks after hydrocortisone.**

***b*, Effect on tenderness. Significant improvement lasted six weeks after hydrocortisone and hydrocortisone T.B.A.**

***c*, Effect on walking time. Significant improvement lasted four weeks after hydrocortisone T.B.A. and two weeks after hydrocortisone.**

***d*, Effect on range of movement. Probably significant improvement lasted eight weeks after hydrocortisone T.B.A. compared with only barely significant improvement for two weeks after hydrocortisone.**

***e*, Effect on limitation of extension. Significant improvement lasted eight weeks after hydrocortisone T.B.A., and 6 weeks after hydrocortisone.**

The trial consisted of three courses (hydrocortisone, hydrocortisone T.B.A., and placebo) each of four fortnightly injections, with eight weeks' rest between treatments. Dosages of hydrocortisone T.B.A. and hydrocortisone were 25 mg. (1 ml.). Placebo (1 ml.) was the vehicle used as the suspending and preserving agent for the T.B.A. compound. The order of courses in each patient was randomised from a master sheet on which names were entered consecutively. Injections were given by one of us (G. N. C.) and assessments made every two weeks throughout both the injection and rest periods by the same physician (V. W.). The nature of the injections was unknown both to the patient and to the assessor.

The fortnightly assessments comprised measurements of: erythrocyte-sedimentation rate (E.S.R.) walking time over 75 yards; range of joint movement and limitation of extension determined by a goniometer (judgment of joint movement by eye must introduce an important source of error and should be abandoned in favour of more accurate measurement); tenderness (graded 0 = none, 1 = slight, 2 = definite, 3 = patient winces, 4 = withdrawal and/or exclamation); pain (graded 0 = none, 1 = slight on walking, 2 = pronounced on walking, 3 = pain at rest, 4 = severe pain at rest).

Radiographs of the knees were obtained before and after the trial.

Results

6 patients failed to complete the trial. 1 defaulted after the second course of injections, 4 required admission to hospital after two courses had been given because of deterioration of arthritis, and 1 developed unrelated disease soon after the trial began. Withdrawals were scattered evenly throughout the random groups.

The specific data (walking time, &c.) derived from the first assessment in each treatment period were compared with the same measurements made at the four assessments in the succeeding eight-week rest period. Changes in pain and tenderness were evaluated from difference in grading; changes in walking time and joint movement were estimated as a percentage of the pre-treatment measurements; change in limitation of extension was recorded as a percentage of maximal joint range (145°). In this way the effect of treatment, both immediate and sustained, was calculated for each of the three treatments in every patient. The mean change for each group (hydrocortisone, hydrocortisone T.B.A., and placebo) between pre-treatment assessments and each of the four post-treatment assessments was analysed by conventional statistical methods (difference of means of unpaired data).

Pain

Significant relief of pain lasted four weeks in patients who had received hydrocortisone T.B.A., compared with two weeks in patients who had received hydrocortisone (fig. *a*). Though greater relief was experienced from hydrocortisone T.B.A. than from hydrocortisone the difference was not significant at any assessment.

Tenderness

Significant improvement in joint tenderness lasted six weeks with both drugs. Probably significant improvement was still present at the eighth week after hydrocortisone (fig. *b*). The difference between the two drugs was not significant.

Walking Time

Significant benefit lasted four weeks after hydrocortisone T.B.A., compared with two weeks after hydrocortisone (fig. *c*). Except at the first assessment, improvement was greater in patients who received hydrocortisone T.B.A., but the difference between the two treatments was not significant.

Range of Movement

Probably significant improvement lasted eight weeks after treatment with hydrocortisone T.B.A. Improvement from hydrocortisone was barely significant at the second week and thereafter became insignificant (fig. *d*). There was no significant difference between the two drugs.

Limitation of Extension

Significant improvement lasted eight weeks after hydrocortisone T.B.A. compared with six weeks after hydrocortisone (fig. *e*). There was no significant difference between the two drugs.

E.S.R.

There was no significant change in E.S.R. as a result of treatment. Throughout the period of study there was a gradual rise in mean E.S.R. which was unaffected by the order in which treatments were given.

Subjective Assessment

The 18 patients who completed the trial were asked to state which course of injections had helped them most. 6 preferred hydrocortisone T.B.A., 4 placebo, and 1 hydrocortisone. 7 ranked hydrocortisone T.B.A. and hydrocortisone equal and preferred these to placebo.

Complications

2 patients experienced local exacerbation of arthritis, lasting one and three days, after injections of hydrocortisone T.B.A. 3 patients developed deep-vein thrombosis in the injected leg (2 after hydrocortisone and 1 after placebo).

Discussion

This trial was planned to assess the comparative value of hydrocortisone acetate and hydrocortisone T.B.A. in the local treatment of rheumatoid arthritis. Improvement from treatment was measured by fortnightly assessments of pain, tenderness, walking time, range of movement, and limitation of extension. On these criteria both drugs showed a significant advantage over placebo. Except in the case of joint tenderness, hydrocortisone T.B.A. gave greater improvement which was of longer duration than that from hydrocortisone, but the difference between the effect of the two drugs was not significant in any instance. It is possible, but unlikely, that larger numbers might show a more definite benefit that would support the claims made for the greater effectiveness of hydrocortisone T.B.A. Hydrocortisone had a slight advantage over the T.B.A. preparation in relief of joint tenderness, but this also was not significant. The random order in which the three courses of injections were given neutralised the expected advantage of first treatment and could not be held to account for the differences observed.

There was no consistent or significant change in E.S.R. that could be ascribed to the effect of any particular treatment, so local improvement was presumably independent of any systemic action. No important side-effects were encountered apart from transitory post-injection exacerbation of symptoms in 2 patients after injection of hydrocortisone T.B.A.

The conflicting claims made for the relative effectiveness of intra-articular injections of hydrocortisone and hydrocortisone T.B.A. (Hollander et al. 1955, Duff 1956, Zuckner et al. 1956) almost certainly reflect failure to conduct trials under controlled conditions. Fearnley et al. (1956) described a pilot study of intra-articular procaine and hydrocortisone acetate in rheumatoid arthritis which explored the possibilities of a crossover design for evaluating differences between drugs. Similar methods, with the additional advantage of a double-blind procedure, have been used in this investigation. Such conditions are an essential prerequisite for the proper assessment of treatment in a disease where bias and chance have so commonly led to favourable reports on remedies now discarded.

Summary

The effects of intra-articular injections of hydrocortisone acetate and hydrocortisone tertiary butyl acetate (T.B.A.) have been studied in 24 patients with rheumatoid arthritis whose main incapacity arose from involvement of the knees.

Each patient was given three courses of injections (hydrocortisone, hydrocortisone T.B.A., and placebo) in random order. Each course consisted of four injections at fortnightly intervals, with eight weeks' rest between courses. Pain, tenderness, walking time, range of joint movement, and limitation of extension were assessed every two weeks. Neither the patient nor the assessor was aware of the nature of the injections in any course.

Both drugs showed a significant advantage over placebo. Improvement was generally greater and of longer duration with hydrocortisone T.B.A. than with hydrocortisone, but the difference was not statistically significant.

We are indebted to Messrs Merck, Sharp & Dohme for a generous supply of hydrocortisone T.B.A. We are grateful to Sister P. R. Benson and her nursing staff for their cooperation.

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DELETERIOUS EFFECT OF INTRA-ARTICULAR HYDROCORTISONE

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IN a controlled trial of intra-articular steroid therapy in rheumatoid arthritis, both hydrocortisone acetate and hydrocortisone tertiary butyl acetate (T.B.A.) were found to give significant clinical improvement lasting several weeks (Chandler et al. 1958a). Four injections of each drug and four of placebo were given into the knees over a period of forty-eight weeks during which physical grading and functional capacity were measured every fortnight. Both drugs showed a significant advantage over placebo; but we were disturbed to find that, despite the generally good clinical response to injections of hydrocortisone and hydrocortisone T.B.A., radiological deterioration, sometimes considerable, had occurred in the knees of over half of patients so treated. We report here the radiological findings and consider the possible mechanism by which deterioration occurs.

Investigation

Radiographs of the knees (anteroposterior and lateral) were obtained before and after treatment in the 18 patients who completed the trial. Twenty-five joints were injected and the X-ray appearances graded into five categories of severity for each feature of the rheumatoid

Fig. 1—Case 5: Radiographs of left knee (*a*) before and (*b*) after treatment. Second radiograph shows distinct increase of joint damage by erosion, and further loss of joint space.

Fig. 2—Case 20: Radiographs of right knee (*a*) before and (*b*) after treatment. Second radiograph shows further notable increase in joint damage by erosion.

process (porosis, lost of joint space, and erosions), together with an overall rating as suggested by Kellgren and Lawrence (1957). 13 joints—just over half—showed radiographic deterioration. Definite worsening occurred in 8, distinct deterioration in 3, and severe deterioration in 2 (table I).

Examples of deterioration are shown in figs. 1 and 2.

The data were then analysed to determine whether any correlation existed between the clinical response to treatment and radiological deterioration. The changes in the initial and final clinical assessments of joint conditions were graded into three categories—improved, unchanged, worse—and considered in relation to radiological change.

TABLE I—RADIOGRAPHIC FINDINGS IN 18 CASES BEFORE AND AFTER TREATMENT

Case no.	Joint	Grade before treatment				Grade after treatment				Deterioration
		Porosis	Joint space	Erosion	Overall grading	Porosis	Joint space	Erosion	Overall grading	
1	L	2	1	0	1	2	1	2	2	+
2	R	1	1	1	1	1	2	2	2	+
	L	1	2	1	1	1	2	2	2	+
3	L	1	2	2	2	3	2	3	3	+
4	R	3	2	2	2	2	2	2	2	0
5	R	2	4	4	4	3	4	4	4	0
	L	1	3	1	2	4	3	4	4	+++
6	R	3	2	1	2	3	2	1	2	0
	L	3	2	0	2	3	2	0	2	0
7	R	1	2	2	2	2	2	2	2	0
9	R	1	0	0	0	1	0	0	0	0
10	R	2	3	1	2	2	3	2	3	++
	L	1	2	0	1	2	2	1	2	+
11	R	3	2	2	2	2	3	3	3	++
14	R	2	1	1	1	2	2	2	2	+
	L	2	2	2	2	2	2	2	2	0
15	R	2	0	1	1	2	0	2	2	+
16	L	2	0	0	1	2	0	0	1	0
17	R	0	0	0	0	0	0	0	0	0
	L	0	0	0	0	0	0	0	0	0
19	R	2	2	2	2	2	2	3	3	+
20	R	1	2	1	1	3	2	4	3	+++
	L	2	2	1	1	3	2	3	3	++
23	L	3	3	4	4	3	3	4	4	0
24	L	2	0	2	2	0	0	2	2	0

Grading of radiographic changes: 0=normal; 1=doubtful; 2=minimal; 3=moderate; 4=severe.
Deterioration in joint condition: 0=none; +=definite worsening; ++=much deterioration; +++=gross deterioration.

Fig. 3 shows that, as might be expected, the group of patients without radiological deterioration contained a larger number of good responses (10 out of 12 joints) than the group in which deterioration had occurred (7 out of 13). The difference was not important ($\chi^2=80$, $P=0{\cdot}4$) and indicated that there was no significant association between overall clinical response and radiological change. In each radiological group 1 patient deteriorated clinically.

The three most useful measurements of joint function (pain, walking time, range of movement) were considered separately in relation to radiological change. Immediate and sustained improvement in clinical status after each course of treatment with hydrocortisone and hydrocortisone T.B.A. were estimated at the second and sixth weeks. Mean improvement in pain was calculated from the difference in grading; mean improvements of walking time and range of movement were estimated as a percentage of pre-treatment measurements. Since the curve of improvement in these criteria of joint function followed the same pattern after both treatments the data deriving from the effect of each were considered together in relation to radiological change (table II).

There was no significant difference in the amount of improvement of pain and range of movement between the group of patients in whom radiological deterioration occurred and the group in whom no such change was observed. At the second and sixth weeks after treatment relief of pain was greater in the group who showed radiological deterioration, but the difference was not significant. Only in respect of walking time was a significant difference apparent. A tendency at the second week to greater improvement in the group with radiological deterioration became definitely significant at the sixth week ($P=0{\cdot}01$). Range of movement showed greater improvement in the group without radiological worsening of disease, though this was not significant.

Discussion

Undoubtedly the intra-articular injection of hydrocortisone and hydrocortisone T.B.A. into the knees of patients with rheumatoid arthritis leads to clinical im-

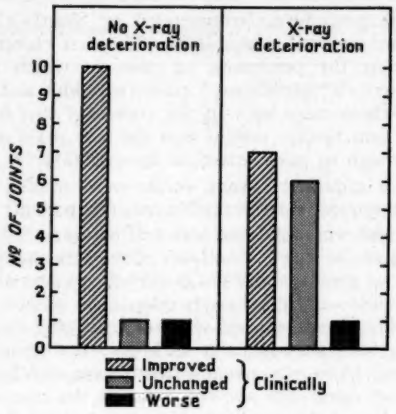

Fig. 3—Relation of clinical response to radiological change.

provement which is encouraging to the physician and appreciated by the patient. Nevertheless in this series of patients who took part in a controlled trial of these compounds radiological deterioration, often considerable, was observed in over half. This disturbing and unexpected finding could be held to result from inevitable progression of disease, but two pieces of evidence are contrary to such an interpretation. First, the group of patients who showed unmistakable and often severe radiological deterioration on the whole fared only slightly less well, judged by clinical criteria, than the group in whom no advance in the radiographic features of arthritis occurred. Secondly, the experience in the Empire Rheumatism Council (1955) trial of aspirin and cortisone in rheumatoid arthritis was that radiological deterioration in the large joints did not occur in a year's observation; with scarcely an exception radiological changes were limited to the small joints of the extremities. The implications from the present study are definite. Intrasynovial injections of hydrocortisone and related compounds either failed to halt or, more usually, accelerated pathological changes, despite the clinical relief enjoyed by the majority of patients.

This apparent paradox of worsening disease in the face of clinical improvement was subjected to further investigation by analysis of the data derived from the various clinical assessments of joint function. No significant association could be traced between the effects of treatment on pain and range of movement in the two groups of patients with and without radiological progression of arthritis. An important difference between the groups was, however, apparent in respect of walking time; a trend towards greater improvement at the second week after treatment in the group with deterioration became very significant at the sixth week. It must be concluded that the principal effect of treatment in this group has been the attainment of a standard performance beyond the capacity of the joint. The discrepancy between the effects on pain and walking time in the two groups is probably more apparent than real. Walking time is to be preferred as a measurement of improvement, for the quantification of pain is notoriously imprecise. The fact that it was not until the sixth week after treatment that improvement of walking time became significant in the group with radiological deterioration suggests that sustained relief rather than immediate improvement is the damaging factor.

TABLE II—EFFECT OF TREATMENT ON JOINT FUNCTION RELATED TO RADIOGRAPHIC CHANGE

Factor	Weeks after treatment	Mean improvement		Standard error of difference of means	P
		Group with X-ray deterioration	Group without X-ray deterioration		
Pain*	2	1·52	1·29	±0·38	<0·6
	6	0·88	0·67	±0·37	<0·6
Walking time†	2	7·0	4·7	±2·43	<0·4
	6	8·5	0·2	±3·1	<0·01‡
Range of movement	2	7·7	8·5	±2·96	<0·8
	6	6·1	6·6	±3·09	<0·9

* Improvement in pain calculated by difference in grading.
† Improvement in walking time and range of movement calculated as a percentage of pre-treatment measurements.
‡ Definitely significant.

The evidence is very convincing that treatment with intra-articular hydrocortisone compounds is potentially dangerous; its very success carries with it a threat of accelerating joint destruction. We have reported elsewhere (Chandler et al. 1958b) the production of a virtual Charcot's arthropathy in an osteoarthritic hip treated over an eighteen-month period by monthly injections of hydrocortisone. This patient had obtained almost complete relief from pain when treatment was discontinued. Indeed the symptomatic benefit experienced by patients may lead to a vicious circle of dependence despite worsening disease. By a local mechanism in which functional improvement and relief from pain are the most important features, it seems likely that interference with the normal protective processes natural to inflammatory disease encourages a degree of weight-bearing and mobility which is inherently traumatic. Dangerous progression under these circumstances might well be expected, and has been our experience in this study. Strict radiological supervision is essential if intra-articular administration of hydrocortisone and related compounds is to retain its place in the rehabilitation of the chronic rheumatic patient.

Summary

18 patients with rheumatoid arthritis whose chief complaint was ascribed to involvement of the knees completed a trial of the effects of intra-articular injections of hydrocortisone acetate and hydrocortisone tertiary butyl acetate. 25 knees were treated.

Radiographs of the knees were obtained before and after the trial, in which physical grading and functional capacity were assessed every two weeks.

Radiological deterioration was observed in 13 joints despite significant clinical improvement in the majority.

Only in walking time was a significant difference apparent between patients who deteriorated radiologically and those who did not. Improvement in walking time was significantly greater in the first group. This group also showed a somewhat greater relief of pain after treatment, but this difference was not significant.

The chief cause for radiological progression was the encouragement of a damaging level of performance by interference with a normal, locally protective mechanism.

We are indebted to Prof. S. J. Hartfall for permission to study these patients and for helpful criticism.

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BARIUM MEAL AND FOLLOW-THROUGH

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Haudek (1912) observed that, if there was a considerable residue in the stomach six hours after a contrast-medium meal, this was good evidence that a disorder was present. This was not a particularly challenging or arresting statement, but for some reason it struck a responsive chord. A six-hour residue. Here was something concrete—or very nearly concrete, bearing in mind the horrible mixtures of bread and bismuth which patients were called upon to swallow in those distant unlamented days. In the succeeding forty-four years all else has changed, but not the concept. To a surprising extent the medical profession is still ready to shake a wise head over a six-hour residue and set about putting it to rights. Haudek may have been largely forgotten but this is his true memorial—a niche in the hall of fame as lasting as that other niche which shows with such satisfactory clarity on the lesser curves of our gastric-ulcer patients.

In modern practice the six-hour residue has a significance in that it is linked with the idea of a barium meal and follow-through. This is a very easy examination to ask for but not at all an easy examination to do, and it is one which is regarded with something like dismay in most X-ray departments. If it is merely a matter of recording the presence or absence of a six-hour residue this is one thing, but generally the follow-through has no such clear-cut target. The doctor demanding it may have made the request simply in the form of a catch-phrase, but even when this is not the case the intention is often obscure and it is left to the radiologist to do as little or as much as he thinks fit. Such examinations are difficult to fit into appointment systems, and in departments where several radiologists are employed on a sessional basis the want of continuity is an additional drawback. The short answer is that "barium meal and follow-through" when asked for in a routine way is likely to prove an unsatisfactory business.

Radiologists have recognised this from early times, and various routines have been introduced in an effort to get over some of the difficulties. One such is the double-meal technique, of which Haudek himself was an advocate but which as often as not has no other result but to make confusion worse confounded.

These are perhaps somewhat controversial views, but they are held by many radiologists and for this reason it was thought worth while to see how far they could be supported and to examine critically the significance of Haudek's six-hour residue. Not much has been written on these lines. Shanks (1952) makes several references to Haudek's work and concludes that a six-hour residue, if of considerable size—say one-fourth to one-third of the meal—is usually of pathological import, but that even then it may be due merely to gross hypotonia and ptosis. This is fair comment, but it still leaves the issue somewhat in doubt. It was with this feeling that the work on which the present paper is based was undertaken.

Method and Material

In the circumstances it did not seem appropriate to introduce a new routine, since the object was to check the usefulness of the ordinary everyday examination. From the start, however, a special ledger was opened and all the patients in the series were put through the greater part of the procedure recommended by Shanks (1952) for full barium-meal examination. The first object was to determine the percentage of cases in which there appeared to be a "significant" six-hour residue and later to follow these cases up. In the course of this it was hoped to gain further insight into the true place of the follow-through in gastrointestinal investigation.

In all, a thousand barium meals were studied and, making allowances for re-examination, 866 patients were included. All were seen and screened before and during the taking of the meal. Five basic films were exposed—two erect, an erect serial of the duodenal cap, one supine, and one prone—and if necessary other films as indicated. All the patients were seen and screened again after an hour, and finally films were taken at six hours. A routine dose of 'Raybar' 16 oz. was given. Patients were seen fasting. No food or drink was allowed between the immediate examination and the one-hour stage, but, again following the technique described by Shanks, a light lunch was permitted before the six-hour film.

When this plan was made it was recognised that the routine was not exhaustive. It was, however, chosen as a compromise which would see the head of the meal into the proximal colon in most cases and allow a view of the often-important ileocæcal region. In a large number of cases the meal was followed further in an attempt to study the whole colon, but since this was not always done the results were not included in the record.

Cases referred were in three categories—(1) hospital inpatients, (2) hospital outpatients, and (3) patients referred direct by their family doctors—and thus gave a very representative cross-section.

Results

A preliminary simple breakdown is interesting (see table I).

The initial examinations in the series were done between August, 1949, and April, 1951, and by a coincidence Gryspeerdt (1951) was working on a similar series at the same time but to a somewhat different end. In the composition of the two sets of patients the main difference is that, whereas at Bromley the sexes were very evenly matched (439 males as against 427 females), in Gryspeerdt's series males outnumbered females in the proportion of 692 to 308. Gryspeerdt found positive evidence of abnormality in 53·9% of his cases, compared with 55·6% in my own series. Taking the most common disease conditions the findings compare as shown in table II.

In the present series a percentage of 9·4 diagnosed as query duodenal ulcer may seem unsatisfactory, but in the interpretation of what are after all no more than shadows there must often be room for doubt. In barium-meal examinations many duodenal caps appear at some stage or other perfectly normal and can be classed as such. The absolutely unequivocal recognition of a duodenal ulcer

TABLE I—PRELIMINARY BREAKDOWN

Disorder	Whole series	Male patients	Female patients
Nil	387	165	222
Gastric ulcer	59	31	28
Duodenal ulcer	210	137	73
Query duodenal ulcer	84	51	33
Carcinoma	17	9	8
Hiatus hernia	32	10	22
Others	77	36	41
Totals	866	439	427

TABLE II—COMPARATIVE FINDINGS IN TWO SERIES OF 1000 BARIUM-MEAL EXAMINATIONS

Disorder	Gryspeerdt (1951)	Present series
Gastric ulcer	17·4%	6·5%
Duodenal ulcer	25·1%	24·0%
Query duodenal ulcer	—	9·4%
Carcinoma	3·3%	1·8%
Hiatus hernia	1·1%	3·8%

is much rarer—as, for example, when an ulcer is shown barium-filled *en face* at the point of convergence of mucosal folds. By far the greater number of duodenal ulcers must be diagnosed on indirect evidence. Often this evidence is perfectly satisfactory, but there still remain the other cases (in this series 9·4%) where a conventionally normal cap cannot be shown and where at the same time a lesion cannot be sworn to. Often minor anatomical variations—for example, of the mesentery or of the gastroduodenal artery—are to blame, or the duodenal loop may be taking an independent course with confusing results.

Despite these minor differences there is quite a lot of agreement between the two series, and the results compare closely enough with those of other workers to echo a general pattern of gastrointestinal frailty.

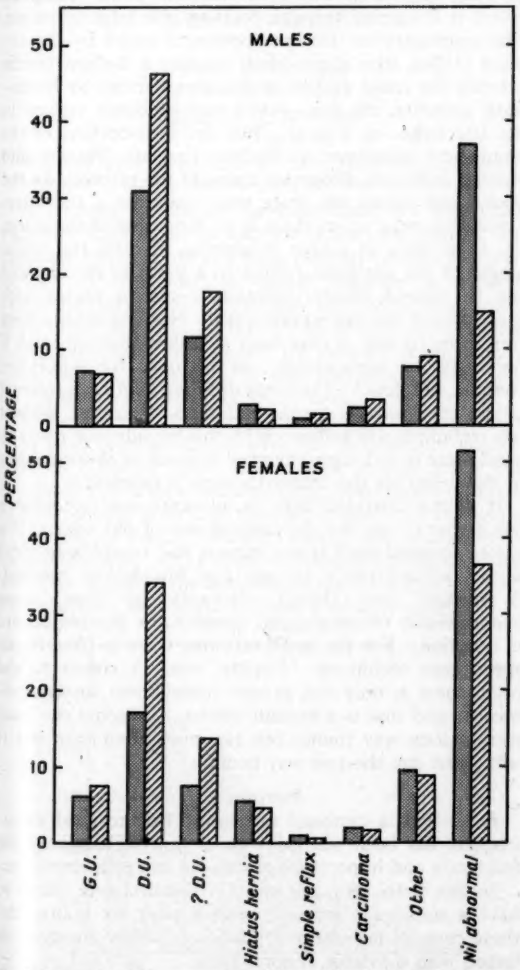

Fig. 1—Prevalence of common conditions (%) at initial examination (stippled) and in cases submitted to follow-up examination (cross-hatched).

As regards the specific question of a six-hour residue two special steps were taken in each case. First, when the patient was screened at the one-hour stage the amount of barium remaining in the stomach was roughly estimated. A guess was made (in writing) as to whether or not there would be a significant residue at six hours, and finally this was checked by the six-hour film. For record purposes a quarter to a fifth of the meal remaining in the stomach at six hours was regarded as significant. Admittedly a guess made in this way is not evidence.

TABLE III—RESULTS OF A FOLLOW-UP ON 215 PATIENTS WHO HAD EARLIER BEEN SHOWN TO HAVE SLOW STOMACH EMPTYING

Group	Males	Females	Totals
No dyspepsia and cases normal at repeat barium meal	26	44	70
Chronic peptic ulcer	24	28	52
Partial gastrectomy for peptic ulcer ..	23	9	32
Other gastrointestinal lesions proved at operation	7	8	15
Dyspepsia continuing: check refused ..	—	3	3
Deceased	6	5	11
Failed follow-up	12	20	32
Totals	98	117	215

However, for as long as medicine remains in some degree an art, impressions will be important and it was my conclusion that a practised observer could forecast a six-hour residue accurately in more than 85% of cases. Among those cases in which the residue was found it was clear that slow emptying and pathology did tend to run together in certain conditions. This is shown graphically in fig. 1, in which the sexes are treated separately. The figure records the prevalence of the common conditions in the whole series and, alongside, the comparable figure in the six-hour residue cases which later constituted the follow-up.

For both men and women the trend is similar. Duodenal ulcers and query duodenal ulcers constitute a much higher percentage of the total in the excess-residue group than in the series as a whole. Conversely the percentage of normal is much higher (especially in males) in the full series than it is in the follow-ups. Elsewhere there is little to choose. It would seem therefore that only in the duodenal-ulcer cases is there a demonstrable link, and this is, of course, what one would expect.

The Follow-up

Further to the initial analysis outlined above an attempt was made to follow up the excess-residue cases in the hope partly of checking the X-ray diagnosis and partly of assessing progress.

There were 215 follow-up cases—98 males and 117 females. The follow-up was done as a running investigation, some of the patients coming to operation within a few days of being first seen and others having had their further barium meals as late as 1957. Great difficulty was experienced in tracking down many of the patients, and when the search was abandoned in 1957 thirty-two of the original total (12 men and 20 women) had not been traced. Of the others the survivors were either re-examined by barium meal or communicated with directly or through their family doctor. A large group—15 men and 25 women—had no dyspepsia and sensibly refused another barium meal, but only 3 refusals were met with from patients still complaining. The large number who came to gastrectomy is striking. The main findings are summarised in table III.

Of the total followed up 38·2% were regarded as not having any significant upper-gastrointestinal abnormality. The percentage of males in whom findings were normal was little more than half the comparable percentage in females. This is probably no more than an echo of the fact, demonstrated by the initial examinations, that slow stomach emptying is more of a female than of a male characteristic. The percentage of normals was smaller for both sexes in the follow-ups than in the whole series, as is shown in fig. 2.

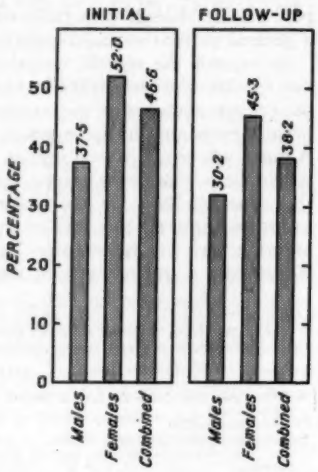

Fig. 2—Prevalence of normal findings (%) at initial examination and in cases submitted to follow-up examination.

Discussion

The results of this investigation may be considered first in relation to slow stomach emptying and secondly in relation to the usefulness of follow-through techniques in general.

Slow Emptying

Stomach emptying certainly cannot be said to follow any simple set of rules. The anatomy is straightforward enough and can be checked in any textbook, but physiology is very different. The digestive work of the stomach is secretory and motor, and any study which fails to take both these factors into consideration is not likely to be conclusive. This is emphasised by Hunt and Spurrell (1951), who claim that for a true estimate of gastric function a simultaneous quantitative record of secretory and motor activity during the passage of a meal is necessary. They state that this can be made by their "serial meal" technique in which a series of standard meals is given, each being terminated by total withdrawal after different intervals of time. Where the barium meal clearly fails is in providing a record only of the results of stomach motility.

As well as being complex in nature, stomach emptying is difficult to control artificially, largely because of the whim of the pyloric sphincter. From a practical standpoint it would help greatly in the interpretation of equivocal pyloric abnormalities if relaxation could be brought about and quick emptying assured. Roka and Lajtha (1950) claim to achieve this control by means of oral procaine, but personal experiences with this method have been disappointing. Methanthelinium ('Banthine') has a limited application, and Chapman et al. (1953) have shown how barium follow-through examinations can be used to check and compare the action of drugs (including methanthelinium) on the propulsive activity of the stomach.

In the final analysis Haudek may be said to be broadly supported. Organic disease, especially peptic ulceration, will lead to slow emptying because of either spasm at the pylorus or stenosis. There is one other well-defined group of slow emptiers: these patients have the normal hyposthenic type of stomach, but with a relatively immobile high duodenal cap—a cap, in fact, in the position usually described in textbooks of anatomy. If this group are kept up and about, emptying may be very slow; but their normality is shown by the ease with which emptying will occur in the recumbent position, especially prone and oblique.

From the point of view of everyday practice it is important to know that delayed emptying from whatever cause can usually be recognised at the initial examination, or failing this within an hour. Further radiographs to prove the obvious are unnecessary.

The Follow-through

Quite a strong impression has been gained from a study of this series that little help towards a diagnosis is ever likely to come from screening or films at one hour or at six hours. Furthermore when the follow-through is carried on to twenty-four or forty-eight hours it is usually equally disappointing. The examination is wasteful of time, energy, and material, and might well be abandoned as a routine test.

This judgment calls for some elaboration in view of the long-held belief that a barium meal is not complete unless it is carried through to show the large intestine. The arguments for this have been well stated by Douthwaite (1956), who claims that, because a barium enema overfills the colon and irons out irregularities by hydrostatic pressure, the large bowel may be better viewed in the late stages of a meal. But the introduction of the tannic-acid technique for barium enemata (Harper and Hughes 1950) has altogether changed the picture. In the tannic-acid enema the stage which matters is the after-evacuation stage where there is no distension of the colon. On these films in a high proportion of cases the whole length of the gut from cæcum to a point in the sigmoid can be viewed empty, contracted, and in spasm with every fold of the mucosa illustrated. Nothing approaching this in usefulness is ever seen at follow-through, and if necessary air replacement can be used for additional contrast and detail. The stage of filling is of little interest unless the lesion is gross—and then, of course, almost any technique will suffice. With this big advance ready to hand there is no longer any need to guess at abnormalities in the colon on the follow-through appearances.

It is not intended here to advocate new techniques but rather to ask for the rational use of old ones. The gastrointestinal tract is too various and complex to yield up its secrets easily to any one blunderbus method. A barium meal should obviously be done when abnormalities of œsophagus, stomach, or duodenum are in question. For the small intestine there is likewise an appropriate technique. Finally, when it comes to the colon there is only one proper complement to sigmoidoscopy, and that is a barium enema. To some this may seem a long way round, but far more often than not it will prove the shortest way home.

Summary

A series of a thousand unselected barium-meal examinations has been studied with a view to assessing the frequence and importance of delayed stomach emptying.

In this series 98 males and 117 females were found to have a significant stomach residue after six hours, and these patients have been followed up. Slow emptying is linked with duodenal abnormalities.

The barium follow-through is often time-consuming and unhelpful. It should not be done as a routine, and

in particular, it should never be relied on for the demonstration of the large bowel.

I have to thank the X-ray, almoner's, and outpatient departments at Bromley Hospital for assistance with the follow-up, and, in particular, Mrs. C. Davies, Miss N. E. King, and Sister B. Latchford. I received welcome assistance from Mrs. L. F. Steele in compiling the tables and figures.

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SERUM-CHOLESTEROL LEVELS AND BLOOD-PRESSURE OF ALASKAN ESKIMO MEN

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ALTHOUGH the Eskimo has been cited as a race which has little atherosclerosis and yet consumes a high-fat diet (Sinclair 1953), it has also been pointed out that the incidence of atherosclerosis among Eskimos is actually unknown (Keys et al. 1957), since necropsies have almost never been performed. Indeed, in Alaska, most Eskimo death certificates are signed by persons other than a physician. Furthermore, a large proportion of Eskimos do not have a high-fat diet (Scott 1956).

Both the serum-cholesterol level and the blood-pressure level have been associated with the incidence of atherosclerosis (Dawber et al. 1957). The present study was designed to determine whether these variables are different in Eskimo men from what they are in white persons living in the United States. We also wanted information about local differences in the diets of Alaskan Eskimos so that we could decide on the areas where the relationship of diet to cholesterol level might be most profitably studied.

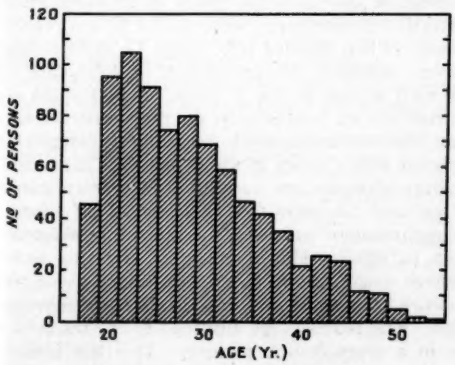

Fig. 1—Ages of men in the study.

CHOLESTEROL LEVELS OF ESKIMO MEN

Age	No. of subjects	Mean	Cholesterol level	
			Standard deviation	Range
17–19	90	187·8	39·1	109–386
20–24	247	201·9	34·9	123–302
25–29	182	219·7	47·1	122–373
30–34	144	219·7	39·1	133–329
35–39	91	233·3	40·1	166–405
40–44	58	234·5	45·5	131–354
45–49	26	243·4	51·4	179–378
50–53	4	200·5	..	186–217

Methods

The subjects were 842 Eskimo men between the ages of 17 and 53 who were members of the Alaska National Guard. No physical examination is required for membership of the Guard, although persons with gross physical abnormalities or active tuberculosis are usually excluded. It was estimated that 80% of the subjects were full Eskimos. Included also were one small group of 28 Aleuts and another of 19 Athabascan Indians. Cholesterol was determined on non-fasting serum by the method of Abell et al. (1952). Twenty-two of the serum samples were sent to the laboratory of the Heart Disease Epidemiology Study, Framingham, Massachusetts, where independent determinations gave results 4·6±1·2 mg. per 100 ml. higher than our results. Blood-pressure was determined in the sitting position.

Results

The mean cholesterol level of all persons tested was 214·4 mg. per 100 ml. with a standard deviation of 40·9 (see table). There was considerable variation of mean cholesterol level depending on geographic location (fig. 2). The highest mean level was 293 mg. (S.D. 64) in 11 subjects, while the lowest mean level was 171 (S.D. 32) in 15 subjects. Men from four of the forty-three villages studied had mean cholesterol levels significantly higher than the average of all Eskimos, while representatives of ten other villages had significantly lower levels, using a 20-to-1

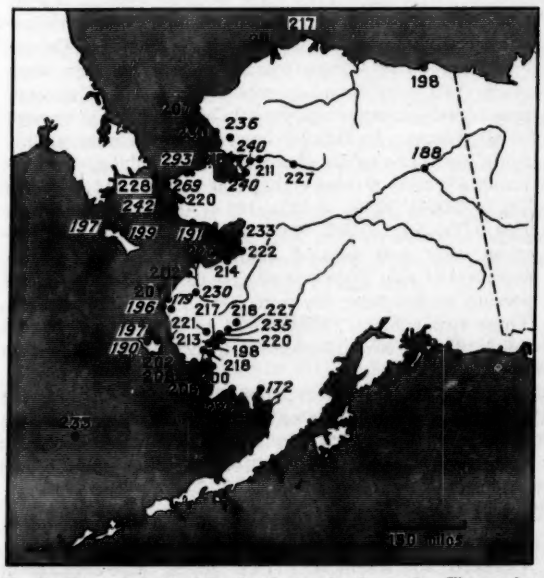

Fig. 2—Mean cholesterol levels of men in the study. Figures in italics are significantly higher or lower than the mean of all subjects.

criterion of significance. The numbers in italics in fig. 2 represent these villages. However, the only generalisation possible from this figure is that northern Eskimos have higher cholesterol levels than southern Eskimos (217·8±2·0 mg. per 100 ml. as opposed to 210·2±1·9 mg.).

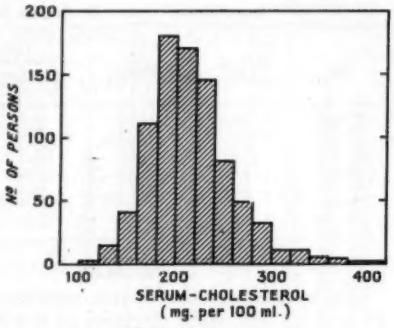

Fig. 3—Cholesterol levels of Eskimo men. Median level is 202 mg. per 100 ml.

There was some dependence of cholesterol level on age (r=0·377). The least squares equation of this dependence was:

$$\text{Cholesterol level} = 158{\cdot}8 + 1{\cdot}97 \times \text{age}.$$

The results shown in the table resemble closely those obtained in normal men in the United States (Lewis et al. 1957). In calculating probability of significance of differences of cholesterol levels, a correction was made for age dependence.

Different blood-pressure readings were obtained by different people, and also by the same person on different days. Our correction for these possible errors may have minimised actual differences between villages. The average systolic pressure found was 126·9, the average diastolic pressure was 74·3, and the average pulse pressure was 52·6 mm. Hg. In further calculations, the mean of the systolic and diastolic pressures was used. The average mean blood-pressure of all men tested was 100·6 (S.D. 10·1).

Of the 842 men tested, 22 had mean blood-pressures above 125 mm. Hg. They came from 16 villages, but no village had more or less persons with high blood-pressure than would be expected from random sampling. Of the forty-three villages from which 10 or more men were tested, four were found in which the men had average mean blood-pressures significantly higher than the average for all villages. In another four, the values were significantly low. The values obtained and probability of significance for each of these eight villages were: 111·6, 0·003; 106·2, 0·004; 105·0, 0·022; 104·4, 0·008; 96·2, 0·010; 95·9, 0·006; 94·6, 0·017; 91·7, <0·0001. That these differences were real seemed evident, since mean blood-pressures of men from two villages measured by the same persons on the same day were 104·4±1·4 and 94·5±2·5. These two villages, though only 14 miles apart, have a quite different ethnic background, and the populations do not intermingle.

There was a low correlation of mean blood-pressure with age (r=0·142). At age 20, mean blood-pressure was 98, while at age 45 it was 104. There was little or no correlation between mean blood-pressure and serum-cholesterol (r=0·066).

Discussion

In the first study of cholesterol levels in Eskimos, Corcoran and Rabinowitz (1937) found these levels to be very low. The mean of 27 determinations was 141 mg. per 100 ml. Subsequent investigations on other small groups of Eskimos (Wilber and Levine 1949, Sinclair et al. 1949, Rodahl 1954a, Pett and Lupien 1958) have failed to confirm these low levels, and are in agreement with our results. Although Alaskan Eskimos as a group appear to have normal serum-cholesterol levels, the geographic variation in level deserves further study.

The measurements of blood-pressure in this study are in essential agreement with, although slightly higher than, those found in a large series of men in the United States (Robinson and Brucer 1939). In any case we, unlike Rodahl (1954b), have found no evidence of unusually low blood-pressures in Eskimos.

Summary and Conclusions

The mean serum-cholesterol level of 842 Eskimo men did not appear to be unusual, but there were significant differences in men from different localities in Alaska. Measurements of blood-pressure showed much less variation, although here again geographic differences were found.

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TYPING OF Q-PHASE INFLUENZA-A VIRUS BY SERUM-NEUTRALISATION TESTS IN MONKEY-KIDNEY CULTURES

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THE method currently used for typing strains of influenza virus is based on hæmagglutination inhibition by type-specific sera. This method is simple and rapid and gives reliable information in the majority of cases. It is not, however, satisfactory for certain strains (Q) which have been described by van der Veen and Mulder (1950). These Q strains combine very poorly with the homologous antibody responsible for inhibiting hæmagglutination and give low titres in hæmagglutination-inhibition tests compared with strains in the reactive or P phase. When injected into ferrets Q-phase strains do, however, stimulate the production of antibodies which react with strains in the P phase, and Q-phase strains are usually typed indirectly by the preparation of an antiserum which is subsequently tested by hæmagglutination inhibition with a strain in the P phase. This method is, however, laborious and wasteful of laboratory animals.

Vogel and Shelekov (1957) described an adsorption-hæmagglutination technique for detecting influenza virus grown in monkey-kidney cultures. By this technique influenza virus is grown in monkey-kidney tissue cultures to which guineapig red blood-cells are subsequently added. The red cells are adsorbed to the infected tissue cells in a characteristic pattern. This has been called hæmadsorption. By this technique we have obtained

TABLE I—SERUM-NEUTRALISATION TESTS IN MONKEY-KIDNEY TISSUE CULTURE WITH STOCK INFLUENZA-A VIRUS STRAINS AND ANTISERA

Virus strain	Serum					
	Shope	PR8	WS	FM-1	A/Ned/36/56	A/Singapore/1/57
Shope	320	<20	<20	<20	<20	<20
PR8	<20	640	80	<20	<20	<20
WS	<20	20	160	<20	<20	<20
FM-1	<20	<20	<20	1280	<20	<20
A/Ned/36/56 ..	<20	<20	<20	40	80	<20
A/Singapore/1/57	<20	<20	<20	<20	<20	2560

The figures denote the reciprocals of dilutions of sera inhibiting 100 hæmadsorption doses of virus.

type-specific serum-neutralisation reactions with strains of influenza virus in both the P and the Q phase.

Materials and Methods

Virus strains.—Standard strains—Shope, PR8, WS, FM-1, and A/Ned/36/56—were received from the World Influenza Centre. Strains isolated in the recent epidemic of Asian influenza were received from various laboratories of the Public Health Laboratory Service; all these strains were isolated in fertile eggs and were received as early passage fluids.

Sera.—Standard sera for the different type strains employed were supplied by the World Influenza Centre. Antisera against some of the Asian-influenza strains were prepared by intranasal inoculation of ferrets with freshly isolated strains.

Monkey-kidney cultures.—Trypsinised cell suspensions were grown for 5 days in stationary tubes with a medium consisting of 0·5% lactalbumin hydrolysate and 0·5% ox serum in Hanks' solution with 100 units penicillin and 100 μg. streptomycin per ml. This medium was then replaced by Eagle's medium (1955) without serum; the cultures were inoculated and incubated in a roller drum.

Virus titrations.—Tenfold dilutions of the virus under test were inocultated in volumes of 0·1 ml. into a pair of monkey-kidney cultures. After 48 hours' incubation 0·2 ml. of a 0·4% suspension of freshly washed guineapig red cells was added. The tubes were kept at room temperature for 10 minutes and then examined under the microscope for hæmadsorption. The end-point was taken as the highest virus dilution showing hæmadsorption.

Serum-neutralisation tests.—Serial dilutions of standard sera in 0·5 ml. volumes were mixed with equal volumes of a virus dilution containing 100 hæmadsorption doses, incubated for half an hour at 37°C and inoculated into tubes of monkey-kidney tissue. These tubes were then sloped in a rack so that the serum-virus mixture was in contact with the tissue cells. After half an hour at room temperature the fluid was removed from the tubes and replaced by fresh medium, and the tubes were incubated in a roller drum for 48 hours at 37°C; 0·2 ml. of a 0·4% suspension of guineapig red cells was then added to the tubes, which were examined for hæmadsorption. The neutralisation titre was taken as the highest final serum dilution showing complete inhibition of hæmadsorption.

Hæmagglutination-inhibition (H.I.) *tests.*—These were performed in 'Perspex' plates using 0·25 ml. volumes of serial dilutions of sera treated with cholera-filtrate to remove any non-specific inhibitors of hæmagglutination, 0·25 ml. of a virus dilution containing 8 agglutinating doses, and 0·25 ml. of a 0·5% suspension of washed fowl cells. The serum dilution showing 50% agglutination was taken as the end-point (World Health Organisation 1953).

TABLE II—COMPARISON OF H.I. TESTS AND SERUM-NEUTRALISATION TESTS WITH STRAINS OF INFLUENZA-A VIRUS IN THE P AND Q PHASES

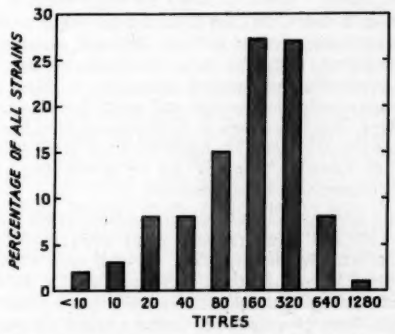
Virus strain	H.I. tests		Serum-neutralisation tests	
	Serum: Q-phase A/England/530/57	Serum: P-phase A/England/550/57	Serum: Q-phase A/England 530/57	Serum: P-phase A/England/550/57
Q-phase A/England/530/57	<10	<10	640	640
P-phase A/England/550/57	320	320	640	640

The figures are the reciprocals of the dilutions of sera.

Results

The results of serum-neutralisation tests with standard strains of influenza-A virus are shown in table I. Cross-reactions were rarely observed, and except for that between PR8 and WS they were of small degree. As in the H.I. tests crossing was not observed between Asian strains and any of the earlier influenza-A viruses.

Table II shows the results of H.I. tests and serum-neutralisation tests with strains of influenza-A virus in the P and Q phase. It will be seen that in the H.I. tests the Q-phase strains did not combine with antibody in sera prepared in ferrets against either P or Q phase viruses, whereas both P and Q strains combined equally well in the serum-neutralisation tests. It is clear from these results that strains in the Q phase may be easily identified by serum-neutralisation without recourse to making a homologous serum. The frequency with which Q-phase strains were encountered in 1957–58 is shown in the accompanying figure. All the tests included in this figure were done with one of the three Asian-influenza ferret antisera with titres varying between 1/160 and 1/320 when tested against A/Singapore/1/57. 21% of 500 strains examined gave titres of 1/40 or less. 10 of these have been tested and successfully typed by the hæmadsorption technique described above.



Frequency distribution of titres of 500 strains of Asian-type influenza-A virus in H.I. tests with A/Singapore/1/57 ferret sera.

Preliminary results of work in progress with human convalescent sera suggest that rises in antibody against Asian influenza are detected more frequently by the hæmadsorption technique than by H.I. tests.

Summary

Asian strains of influenza-A virus in the Q or non-reactive phase, determined by the standard hæmagglutination-inhibition test, can be typed fairly simply by a serum neutralisation test in monkey-kidney tissue culture using the hæmadsorption technique of Vogel and Shelekov (1957).

I should like to thank Dr. F. O. MacCallum for encouragement in this work, and Dr. A. Isaacs (World Influenza Centre) for supplying some strains and sera.

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HYPERPYREXIA IN ENCEPHALITIS TREATED BY HYPOTHERMIA

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SPORADIC cases of encephalitis have an uncertain prognosis, the outcome depending partly on the success of prophylaxis and treatment of the complications of the coma. One feature of the disease which may cause death is hyperpyrexia. A case is here described of encephalitis complicated by rapidly increasing pyrexia in which the temperature was reduced by hypothermia induced by drugs and physical cooling and maintained at a subnormal level until consciousness returned.

Case-report

A lift attendant, aged 30, was admitted on Feb. 12, 1958. Eight days before admission he had had a febrile illness with sore throat and cough, diagnosed as " influenza ". All members of the family had a similar illness at the time. After four days he had recovered sufficiently to resume work. Two days later he complained of pains in the back and was sent home from work at midday. Arriving home he slept from 2 P.M. to 8.30 P.M. on a couch, refused food, did not reply to his wife's questions, and then retired to bed. He made no complaint of headache. That night he was extremely restless in bed, sweated profusely, and shouted several times. Next morning his wife was unable to rouse him and noted that his whole body was shaking. On her return to the bedroom after summoning the doctor she found him sitting on the floor in a pool of urine; he did not recognise her, nor did he answer her questions. He was admitted in a stuporose state.

His past history included partial gastrectomy for a duodenal ulcer in 1953 and deterioration of visual acuity in 1954, owing to familial macular degeneration. At that time a full neurological examination had been performed by Dr. E. A. Blake Pritchard and ophthalmological examination by Mr. C. Dee Shapland; these provided very useful records for purposes of comparison. Since then he had been able to read only with the aid of a powerful hand lens in addition to glasses.

On admission his temperature was 100·4°F; pulse-rate 100 per min., pulse regular; respiratory rate 28 per min. He was very agitated and restless, did not reply to questioning but responded to painful stimuli, and greatly resented physical examination. He had neck rigidity, trismus, and photophobia. His pupils were equal and circular, and reacted to light. His fundi showed bilateral macular degeneration, with optic atrophy on the right side; the disc margins were sharp. No abnormality was detected in the remaining cranial nerves. In his limbs the tone varied from time to time with spontaneous movements; he had continuous muscle twitchings. His tendon reflexes were weak and plantar responses flexor. His respiratory excursion was noticeably shallow and he was cyanosed.

Investigations.—White blood-cells 9800 per c.mm. (polymorphs 70%, lymphocytes 26%, monocytes 4%). Urine normal. Chest X-ray normal. Lumbar puncture yielded cerebrospinal fluid (C.S.F.) under pressure of 300 mm. H_2O (but patient was struggling) containing protein 110 mg. per 100 ml. (globulin, slight excess (Pandy test)), white blood-cells 31 per c.mm. (lymphocytes 30, polymorphs 1); red blood-cells 1 per c.mm.; chloride 700 mg. per 100 ml.; sugar 95 mg. per 100 ml. No bacteria were seen on Gram and Ziehl-Nielsen staining.

Diagnosis and treatment.—The diagnosis was considered to be either acute encephalitis, possibly influenzal, or fulminating tuberculous meningitis. The patient was seen by Dr. W. W. Gooddy, who agreed and advised a further lumbar puncture the following day to see whether by then the C.S.F. sugar and chloride levels had changed. Repeat lumbar puncture on the following morning yielded C.S.F. under a pressure of 300+ mm. H_2O, containing protein 180 mg. per 100; white blood-cells 66 per c.mm. (polymorphs 57%, lymphocytes 38%, monocytes 5%); red blood-cells 9 per c.mm.; chloride 725 mg. per 100 ml.; sugar 58 mg. per 100 ml.

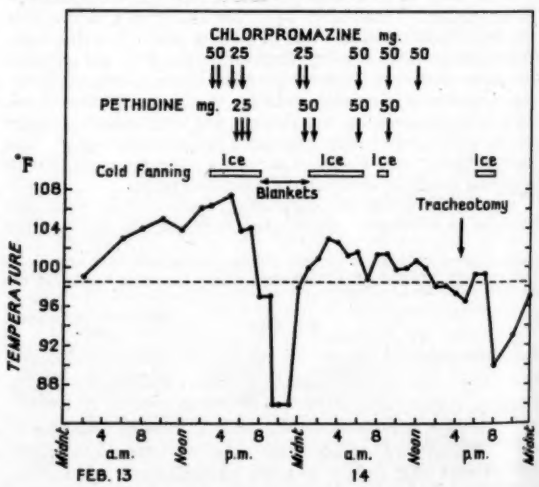
Acute encephalitis was diagnosed and treatment was directed to preventing complications until consciousness returned—particularly of the chest in view of the persistent cyanosis and shallow breathing. An endotracheal tube was inserted to maintain a good airway. A tracheotomy was performed the following afternoon by Mr. B. V. McEvedy.

At 2 A.M. that morning the patient's temperature was 99°F, at 6 A.M. 103°F, at 8 A.M. 104°F, at 10 A.M. 105°F; cold sponging and fanning were instituted. At noon the temperature was still 105°F, by 2 P.M. it had risen to 106·2°F, and by 2.30 P.M. it was 106·4°F. All temperatures were taken rectally.

Induction of hypothermia.—Since the continued rise of temperature seemed likely to prove fatal the decision was made to use hypothermia in an attempt to reduce the temperature to normal. Chlorpromazine alone was given initially (since pethidine was contraindicated by the shallow breathing and cyanosis) and the trunk and limbs were covered with ice. Shivering was not entirely prevented by chlorpromazine, and in the first two hours the temperature did not fall; in fact it rose to 107·6°F at 5.30 P.M. During this period the patient's respiratory excursions improved greatly and his cyanosis lessened. Pethidine was then administered intravenously; in conjunction with chlorpromazine this controlled the shivering and the temperature fell to 97°F by 8 P.M. The ice, ice water, and fans were removed and blankets placed on the patient. Despite this his temperature continued to fall, and an hour later it had reached 86°F. He was then warmed, but his temperature rose to 103°F. With further cooling it fell to 90°F and then rose to 97°F. It was then maintained at 96–98°F until consciousness was regained sixty-five hours after admission. The amounts of drugs given and temperature chart are shown in the accompanying figure.

Further treatment and progress.—During the period of unconsciousness the water and electrolyte balance was maintained principally by means of 2·5% glucose in 0·45% saline solution administered initially through an intravenous needle, but later through a polyethylene catheter inserted in the femoral vein. His urine volume was well maintained after an initial period of oliguria. No cardiac arrhythmias were detected.

After regaining consciousness the patient was very restless, requiring sedatives during the next four days to control his agitation. His behaviour then returned to normal. The tracheotomy tube was removed on Feb. 20.



Temperature and treatment chart during initiation of hypothermia.

Physical examination a week after return of consciousness showed nystagmus to the left. Otherwise there was no abnormality which had not been noted four years previously. He had a retrograde amnesia dating back to about six weeks before the onset of coma; this defect of memory still persisted two months later. He is also forgetful of recent events and complains of lack of ability to concentrate.

Electroencephalography a fortnight after admission showed generalised abnormalities with rhythms down to 4 c.p.s. in the frontal areas. A further examination a month later showed the expected improvement with a stable dominant α rhythm.

Complement-fixation tests performed by the Central Public Health Laboratory, Colindale, on blood specimens, taken on the second day of his illness and three weeks later, were negative for antibodies to influenza A and B, the adenoidal-pharyngeal-conjunctival (A.P.C.) group of viruses, Q fever, psittacosis, and streptococcus M.G.

The patient was discharged on March 17.

Discussion

This illness was probably sporadic encephalitis in a patient who had had an influenzal-like illness two days previously and not "influenzal encephalitis", since antibodies to the viruses of influenza A and B could not be detected in the serum during the acute phase.

The principal purpose in inducing hypothermia was to avert a known fatal complication of encephalitis—namely, hyperpyrexia due to disturbance of the heat-regulating centre. A second purpose was to reduce oxygen consumption in a patient with persistent cyanosis. Both these aims were achieved. The possibility of using hypothermia in the treatment of hyperpyrexia was mentioned by Gray (1957). No reference to its use in the hyperpyrexia of encephalitis has been found. Rowbotham et al. (1957), however, employed hypothermia to reduce cerebral metabolism and prevent death from hyperpyrexia in a case of head injury with a rising temperature; it is also used in neurosurgical procedures.

Shivering was not abolished in this case by chlorpromazine alone; possibly the dosage was insufficient. No cooling occurred while the patient was shivering. Respiratory rate and depth were, however, greatly improved either by the chlorpromazine or by the stimulus of ice on the skin. The addition of pethidine controlled the shivering, and the rectal temperature then fell very rapidly to 86°F (30°C) as the result of skin cooling by ice water. During rewarming the rectal temperature rose to 102°F—not the 96–98°F aimed at. The difficulty of controlling the cooling and warming of this patient emphasises the disadvantages of the technique of achieving hypothermia by skin cooling. This difficulty was pointed out by Khalil and Mac Keith (1954), who advocated the use of an intragastric balloon irrigated with ice water—a method which proved satisfactory in rabbits and in a boy of 16. Khalil (1958) has reported the successful use of this method in the removal of intracranial tumours in two cases.

The reduction of cerebral metabolism is greatest with reduction in temperature to 82°F; below that temperature further cooling results in little decrease of metabolic rate. Stone et al. (1956) showed that shivering causes a pronounced increase in cerebral metabolism, underlining the importance of abolishing shivering in these cases.

In the present case the cause of the shallow breathing on admission was not clear. An endotracheal tube was inserted initially so that respiration could be assisted if necessary. Some difficulty was experienced in removing secretions, and the trecheotomy might have been performed earlier with advantage. Efficient physiotherapy throughout the period of coma and the following days, together with penicillin, averted aspiration pneumonia.

We thank Dr. W. Brooks and Dr. P. J. Verrill for advice with regard to hypothermia, and Sister B. Sowden and the nursing staff of ward 4.

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CHEST PHYSIOTHERAPY DURING INTERMITTENT POSITIVE-PRESSURE RESPIRATION

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THE introduction of intermittent positive-pressure respiration (I.P.P.R.) by Lassen (1953) was an important advance in the treatment of respiratory paralysis. This method was first used in treating cases of poliomyelitis, but its scope has since been extended to include treatment of cases of acute polyneuritis, tetanus, barbiturate poisoning, myasthenia gravis, bronchitis with emphysema, and other conditions. When artificial respiration is required for patients with paralysis of the respiratory muscles, the patient is normally too weak to cough sufficiently to clear the bronchial tree of secretions so that there is a special liability to pulmonary complications.

In the prophylaxis and treatment of these complications, which may well determine the final outcome, physiotherapy to the chest is of prime importance (Lassen 1953, Smith et al. 1954). It is normally given in the form of "vibration" to the chest wall followed by powerful compression of the chest, the whole manœuvre occupying less than one second and being repeated with each breath. The patient is postured to drain the part of the lung receiving treatment. We consider here the mechanisms by which this physiotherapy is effective.

Modern electronic manometers have played an important part in the elucidation of mechanical properties of the chest, and important contributions have thus been made in recent years to knowledge of both normal and abnormal lungs and thoracic cage. In the present investigation manometers of this type have been used to measure the pressure changes in the thorax during artificial respiration with and without chest physiotherapy, and this has thrown light on the mechanism by which chest physiotherapy produces its effect.

Methods

Œsophageal pressure was measured by an air-filled polyethylene tube 1·5 mm. bore, enclosed over the terminal 18 cm. by a latex balloon which tolerated the introduction of 2 ml. air when lax and free before any pressure change. The part of the tube inside the balloon had a hole in its wall every 2 cm. All pressure changes were measured with a capacitance manometer and recorded on a direct writing recorder. Air flow was measured by a modified Lilly (1950) pneumotachograph.

* Work done while holding a Rhodes scholarship.

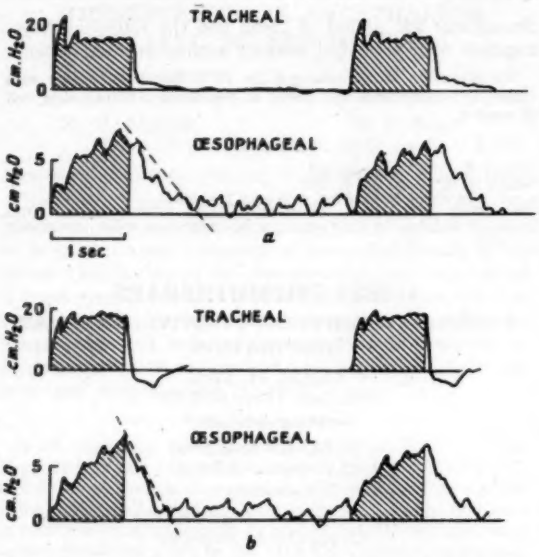

Fig. 1—Pressure in trachea and œsophagus during I.P.P.R. Inspiratory period is hatched. In fig. 1*b* expiration is expedited by short negative-pressure phase, as is shown by slope of dotted line.

In order to determine the air flow in centimetres per second the coronal diameter of the trachea was measured on a radiograph taken in the expiratory position. The diameter of the tracheotomy tube was known, and its apparent diameter was measured on the radiograph. This enabled a correction to be made to the radiographic diameter of the trachea to provide the real diameter. The sagittal diameter was taken to be five-sixths of the coronal diameter (Engel 1947), and the cross-sectional area of the trachea was derived from these figures. Six patients were receiving I.P.P.R. from a 'Radcliffe positive-negative-pressure respiration pump' (Russell et al. 1956); two were on pumps of comparable design but with no negative-pressure phase. Every patient had a tracheotomy with a cuffed rubber tracheotomy tube (Spalding and Smith 1956). The cuff was inflated sufficiently to provide an airtight fit in the trachea. Subatmospheric pressure is referred to as negative pressure.

Results

During inspiration by I.P.P.R. the pressure in the trachea is raised and air enters the lungs. As this occurs and the lungs inflate, the pressure in the œsophagus rises (fig. 1*a*). During expiration the tracheal and œsophageal pressures fall rather steeply provided a satisfactorily free passage is available for the expired air. Expiration may, however, be expedited by a negative pressure in the trachea (fig. 1*b*), and, as this is the pressure pattern we normally use clinically, it has been used during this investigation. The œsophageal pressure is modified during physiotherapy, and fig. 2 shows œsophageal pressures with physiotherapy occurring during inspiration (fig. 2*a*), early in expiration (fig. 2*b*), and in the middle of the expiratory period (fig. 2*c*). Fig. 2*b* and *c* were taken during unusually vigorous physiotherapy, and in normal treatment the œsophageal pressure is raised to a peak of only about 4 cm. water. The timing of the compression varied from one physiotherapist to another. All started at the beginning of expiration. The majority gave a preliminary period of "vibration", followed by forceful compression in the middle of the expiratory period (fig. 2*c*), when they could feel that the chest had virtually returned to the resting position. Others omitted the vibration and compressed during the period of rapid initial deflation in early expiration (fig. 2*b*).

Physiotherapy is usually given with the hands placed close together over the part of the lungs to be treated. Fig 3*a* shows the effect of holding the hands on the posterior and anterior aspects of the chest, another method commonly used. Fig 3*b* shows the effect of pressure on the abdomen only, and Fig. 3*c* of synchronous pressure on the chest and abdomen. This last produces a very pronounced rise in œsophageal pressure, but as it requires two operators it is inconvenient in practice. Fig. 4 shows the effect on the œsophageal pressure of chest compression of the normal duration 0·5 sec., and of a longer period—1·25 sec.

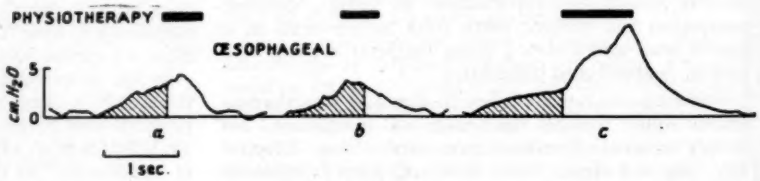

Fig. 3—Effect of less usual types of physiotherapy on œsophageal pressure: (*a*) with hands on anterior and posterior aspects of chest, (*b*) with pressure to abdomen only, (*c*) with synchronous pressure to abdomen and chest.

The rate of air-flow in and out of the lungs is related to the œsophagotracheal pressure, since the œsophageal pressure is closely related to the intra-pleural pressure (Dornhorst and Leathart 1952, Fry et al. 1952). Therefore the rise in œsophageal pressure during physiotherapy (fig. 2*b*) accelerates expiration. A greater and more prolonged alteration in this pressure gradient can, however, be produced by increasing the negative pressure to the trachea during expiration. Fig. 5 shows the maximal negative pressure produced in

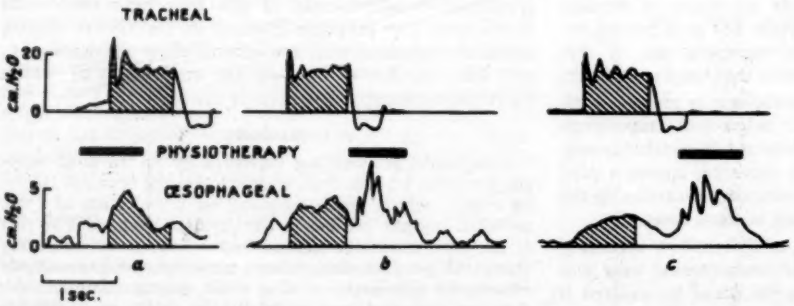

Fig. 2—Effect of chest physiotherapy on tracheal and œsophageal pressure. Compression (*a*) during inspiration, (*b*) at the inspiratory-expiratory junction, (*c*) during middle of expiratory period. Methods (*b*) and (*c*) are normally used. These records show unusually powerful compression.

the trachea and œsophagus by the Radcliffe positive-negative-pressure respiration pump. One of the features of this respiration pump is that negative pressure is produced by gravity and therefore comes into operation without delay. It produces a negative pressure in the trachea of about 10 cm. water so that the œsophagotracheal pressure gradient is greater than that produced by physiotherapy. Moreover, the œsophageal pressure is still raised when this negative pressure is applied to the trachea, so that the pressure gradient is further increased (fig. 5). As physiotherapy usually causes a pressure difference of about 4 cm. water, the negative pressure produced by the pump results in a much greater œsophagotracheal pressure difference.

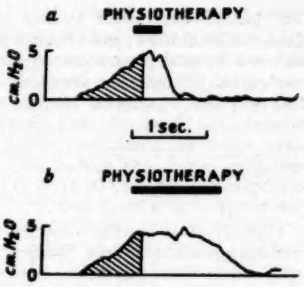

Fig. 4—Effect of duration of physiotherapy on œsophageal pressure : (*a*) brief compression (less than 0·5 sec.), (*b*) prolonged compression (1·25 sec.).

These findings were supported by studies of the air-flow through the tracheotomy tube. The expiratory flow was expedited by negative pressure in the trachea, which increases the flow considerably more than does chest compression given at the inspiratory-expiratory junction. Application of compression later in the expiratory period (fig. 2*c*) caused very slight alteration in air-flow. Maximum air-flow recorded with the positive-negative-pressure respiration pump was less than 2 litres per sec., corresponding to a speed of 16 m. per sec. (51 ft. per sec., 36 miles per hour) compared with speeds close to that of sound in the trachea during normal coughing (Ross et al. 1955).

Discussion

Physiotherapy to the chest is an effective method of removing secretions from the lungs. There are two principal mechanisms by which it may act :

1. By raising the intrathoracic pressure as a whole it causes air to be rapidly expelled from the lungs, and possibly the blast of air thus created carries secretions along, as in the normal cough sputum is carried from the trachea to the exterior.

2. By local compression of the consolidated lung the retained material may be squeezed out along the bronchus, as tooth-paste is squeezed out of its tube. This has been observed during bronchoscopy (A. C. Smith, personal communication).

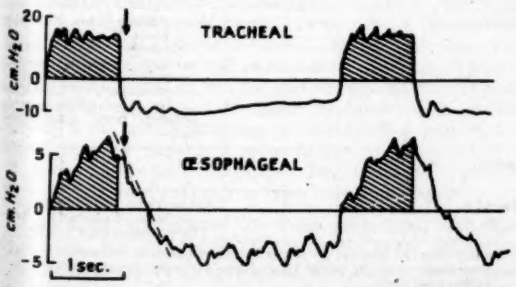

Fig. 5—Tracheal and œsophageal pressures with negative pressure of 7-10 cm. water in trachea throughout expiration. At arrow œsophagotracheal pressure gradient is about 13 cm. water.

For a given part of the respiratory cycle the air-flow is related to the pressure difference between the œsophagus and trachea, and the records (figs. 2 and 5) show that a greater pressure difference and greater air-flow can be produced by the respiration pump than by the physiotherapist. Clinical experience indicates, however, that a negative-pressure phase from a respiration pump is a totally inadequate substitute for chest physiotherapy. The increased expiratory flow with physiotherapy is not even capable of expelling loose secretions through the tracheostome, and endotracheal suction through a soft rubber catheter is necessary to remove secretions when they have reached the larger bronchi. Moreover, physiotherapy during the middle of the expiratory period (fig. 2*c*) is as effective as in early expiration (fig. 2*b*), although the air-flow is very much less. It therefore seems probable that the vital part in physiotherapy of the chest is the direct squeezing of that part of the lung beneath the physiotherapist's hands, and that this pushes the secretions out into the main bronchi. Machines have been designed which are intended to clear secretions from the chest of a paralysed patient, their principle being to inflate the lungs to a considerable pressure and suddenly apply negative pressure to the trachea. This produces a considerable outflow of air in a short time, though probably the flow rate is much slower than in normal coughing (Whittenberger 1957), but it does not simulate the squeezing of a consolidated lobe that appears to be so valuable in chest physiotherapy. This may account in part for the fact that these " cough-machines " have not been more widely adopted.

During normal respiration the intrathoracic pressure is subatmospheric during inspiration, and this assists the return of venous blood to the heart. During artificial respiration by I.P.P.R. (and similar considerations apply to the tank respirator) the pressure in the chest is raised during inspiration, impeding return of blood to the heart (Werkö 1947), and the maintenance of cardiac output may depend on compensatory mechanisms. Physiotherapy to the chest further increases the intrathoracic pressure. In our experience, however, this hardly ever justifies the omission of chest physiotherapy, even in a patient who is very ill and whose compensatory mechanisms are suspect. In such a patient we sometimes give physiotherapy in the horizontal and head-down positions, but omit the head-up position normally used for treating the upper lobes. Clinical experience has shown that each period of chest compression need only be brief, up to about 0·75 sec. (fig. 2*b* and *c*, fig. 4*a*), for prolonged compression appears to be no more effective. For the same peak œsophageal pressure, periods of compression of 0·4 sec. and 1·25 sec. (fig. 4) result in an increase in mean œsophageal pressure of 50% and 200% respectively. The shorter period therefore places a smaller strain on the circulation.

Summary

Physiotherapy to the chest is an effective method of removing secretions from the lungs of patients with respiratory paralysis.

The life-saving benefits of physiotherapy are due to direct squeezing of the part of the lung beneath the physiotherapist's hands, not to a general increase in the rate of expiratory flow.

We wish to thank Dr. W. Ritchie Russell and Dr. A. Crampton Smith for their advice and assistance.

References overleaf

FAMILIAL OUTBREAK OF ACUTE GLOMERULONEPHRITIS DUE TO GRIFFITH TYPE-1 STREPTOCOCCUS

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SHEFFIELD ROYAL INFIRMARY

THE opportunity of investigating, at an early stage, the bacteriology of familial outbreaks of acute glomerulonephritis does not often arise.

We have been unable to trace any report of a family or community outbreak in which infection with the β-hæmolytic streptococcus, Lancefield group A, Griffith type 1, resulted in acute nephritis in as many as four members out of ten affected.

In the familial outbreak of acute nephritis we describe, such a "nephritogenic" action has been demonstrated for a type-1 streptococcus.

History of Outbreak

The family Q consists of father, aged 40, mother aged 38, and nine children aged 17–1½ years. The family lives in a semidetached house with 6 rooms (3 bedrooms) in a large village on the outskirts of Sheffield. None of the family had suffered from scarlet fever, rheumatic fever, or frequent attacks of acute tonsillitis and none had undergone tonsillectomy.

The main clinical and bacteriological features are summarised in the accompanying table. In the first week of February, 1958, Joan Q contracted severe acute tonsillitis. Three to four weeks later her sisters Jane and Mary developed severe attacks of the same illness. The following week John, Martha, Francis, and Rose Q developed mild infections of the upper respiratory tract within a few days of each other. Kenneth Q, the youngest, fell ill with cervical adenitis and acute otitis media after the four preceding children had recovered. Both parents developed sore throats a week after Kenneth had fallen ill, and the mother subsequently had monoarthritis. The only member of the family not to suffer some clinical illness up to this point was the eldest son, Harold. Only Kenneth received systemic penicillin. Some of the others were treated with oral penicillin.

Case 1.—Joan Q was admitted to the Sheffield Royal Infirmary on March 3, 1958, with a history of dyspnœa and passage of dark urine for the past week, and of generalised œdema for forty-eight hours. Anasarca and pulmonary congestion were confirmed; the blood-pressure was raised; and the urine contained albumin, red blood-cells and casts. A throat swab prior to penicillin therapy grew commensals only. The patient was treated by bed rest; restriction of protein, fluid, and salt intake; and systemic penicillin for fourteen days, followed by oral phenoxymethylpenicillin until her discharge on April 4. She was then symptom-free and the blood-pressure had returned to normal, but the urine still contained some albumin, red blood-cells, and occasional hyaline casts. A week after returning home the patient had recurrence of acute tonsillitis, which was treated with oral penicillin. When her condition was reviewed on April 18 a β-hæmolytic streptococcus was grown from a nasal swab.

Case 2.—Her mother informed us that Joan's sister, Jane, had been admitted to the Sheffield Royal Hospital on April 5 with severe acute nephritis. A throat swab taken after three days' penicillin therapy grew only mouth commensals. Jane was treated with systemic penicillin for twenty-three days. Further throat and nasal swabs on April 17 again failed to grow pathogens.

Case 3.—The family doctor sent up a third daughter, Mary, who had developed hæmaturia and facial swelling a week previously. A throat swab after admission (April 18) grew a β-hæmolytic streptococcus. She received the same treatment for acute nephritis as case 1 and was discharged to a convalescent home on May 8.

As soon as it was realised (April 18) that multiple cases of acute nephritis had occurred, the whole family was asked to attend (April 19) for further investigation. The only abnormalities discovered were unilateral conjunctivitis in the mother (present for a month, complicating long-

FINDINGS IN Q FAMILY

Name	Age (yr.)	Interval (weeks)*	Swabs		Clinical sequelæ
			Nose	Throat	
Joan	14	0	0 +	– –	Acute glomerulonephritis
Jane	15	3	0 –	– –	Acute glomerulonephritis
Mary	13	4	0 0	+ –	Acute glomerulonephritis
John	11	5	+ +	– +	None
Martha	8	5	+ +	– +	Symptomless albuminuria with red and white blood-cells and cellular casts in urine (April 19). Repeat urine examination showed trace of albumin, occasional red and white blood-cells, no casts (May 1)
Francis	6	5	+ +	– +	None
Rose	3	5	+	–	None
Kenneth	1½	6	– –	– –	Cervical adenitis and otitis media (β-hæmolytic streptococcus, Lancefield Group A, Griffith type 1, isolated from aural discharge)
Mother	38	8	+ +	+ +	Monoarthritis (E.S.R. 25 mm. in 1st hour, Wintrobe). Conjunctivitis complicating chronic nasolacrimal-duct obstruction (β-hæmolytic streptococcus, Lancefield Group A, Griffith type 2, isolated from conjunctival sac)
Father	40	8	0 –	+ +	None
Harold	17	9	– +	– –	Polyarthritis (E.S.R. 44 mm. in 1st hour, Westergren. Anti-streptolysin titre 1:600)

* Figures refer to interval in weeks between onset of infection of upper respiratory tract in initial case (Joan, 1st week February, 1958) and subsequent cases.
\+ = β-hæmolytic streptococcus Lancefield group A, Griffith type 1 isolated.
– = above organisms not isolated.
0 = no swabs taken.
Swabs were taken from inpatients on admission and after an interval. Swabs were taken from outpatient attenders on April 19 and May 1.

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standing nasolacrimal duct obstruction), an infected nose in Martha, and cervical adenitis with a discharging middle ear in Kenneth. The blood-pressure was measured in all except the two youngest children and was found to be normal. Non-catheter specimens of urine were normal in each case except that of Joan, who had been recently treated for acute nephritis and whose urine still contained some albumin and red-blood cells, and of Martha, whose urine contained a moderate amount of albumin, an excess of red blood-cells, occasional cellular casts, and leucocytes. No other clinical evidence of acute nephritis was obtained in this girl and the urinary abnormality was thought to represent mild acute nephritis. Throat and nasal swabs were taken from all those attending. In addition the mother's conjunctival and Kenneth's aural discharges were cultured. β-hæmolytic streptococci, Lancefield group A, were isolated from one or more sites in all those examined, except Harold.

On May 1 the family was visited at home. We learned that Harold had developed pains in both ankles during the previous week, and was receiving physiotherapy at a clinic. On this occasion his throat swab grew a β-hæmolytic streptococcus, later found to be of Lancefield group A, Griffith type 1. His erythrocyte-sedimentation rate (E.S.R.) was 44 mm. in the 1st hour (Westergren) and his anti-streptolysin titre was 600. Further throat and nasal swabs were taken in six of the others. β-hæmolytic streptococci group A were again isolated from each except Kenneth. The first β-hæmolytic streptococcus isolated from each subject was later typed in the Streptococcal Reference Laboratory, Colindale, through the courtesy of Dr. R. E. O. Williams, and found to be of Griffith type 1, except the streptococcus from Mrs. Q's conjunctival sac, which belonged to type 2. Blood was taken from cases 1–3 and their mother (May 30), and the sera were tested for type-specific antibodies. In each case antibody against type-1 streptococcus was demonstrated, and there was a suggestion that the antibody was more active for the homologous strain than for a stock type-1 strain. There was only slight activity with the sera from cases 1–3 against some type-12 strains—not strong enough to suggest that the nephritis was really due to an inapparent type-12 infection.

Discussion

We feel that this familial outbreak of upper-respiratory infection was caused by a type-1 streptococcus for the following reasons:

1. The organism was recovered from ten of the eleven members of the family within two to nine weeks of the individual initial throat infections.

2. No other types of β-hæmolytic streptococci were isolated from a total of thirty-nine swabs with one exception: that from Mrs. Q's conjunctiva grew a type-2 streptococcus, but she also carried a type-1 in her nose and throat. Harold Q was the only member of the family whose swab failed to grow any streptococci on April 19, and he was the only one who had not by then contracted an infection of the upper respiratory tract. A few days before the second swabbing on May 1, which grew type 1 streptococcus, he contracted polyarthritis.

3. Blood taken from cases 1–3 and from their mother (May 30) contained antibody to type-1 streptococcus.

It has been appreciated for some years that, with few exceptions, the incidence of rheumatic fever following Lancefield group-A streptococcal infection is fairly low and that the attacks are not associated with any specific type (Siegel et al. 1955). In contrast to this, the incidence of acute nephritis, following streptococcal infection varies considerably in different streptococcal outbreaks. In recent years the bacteriology of community outbreaks of acute nephritis has been studied by typing the streptococci isolated from the upper respiratory tract. These studies have shown that in cases of acute nephritis certain types of streptococci are much more commonly isolated than other types. Thus, types 4, 12, and 25 have been incriminated in various parts of the world. A hitherto undescribed type of streptococcus—Red Lake—has been added to the known " nephritogenic " types (Updyke et al. 1955). Infection with other types, including type 1, have been associated only sporadically with acute nephritis. In Great Britain Wilmers et al. 1954 found that of 31 cases of acute glomerulonephritis, treated in various London and provincial hospitals, 28 grew type-12 streptococcus, while the remaining 3 grew types 1, 2, and 3 respectively. In a concurrent investigation in which β-hæmolytic group-A streptococci from 1380 patients were typed, type 12 occurred in 8·2% and type 1 in 10%. They concluded that in Great Britain as in the United States acute glomerulonephritis was closely related to infection with type-12 streptococcus. From their figures no such relationship is discernible for type-1 streptococcus in 1953.

In a large outbreak of streptococcal illness in Wyoming type-1 streptococcus was isolated from 196 patients, but no cases of acute nephritis developed amongst these (Rammelkamp and Weaver 1953).

The Q family outbreak appears to be the first reported in which a high incidence of acute nephritis following type-1 streptococcal infection has been demonstrated. Of the ten affected members of the family three contracted clinical acute nephritis, and a fourth had the urinary changes of acute nephritis without displaying symptoms. This type of renal reaction to streptococcal infection has been described after scarlatina (Harries and Mitman 1947). It is of interest that two of the infected people contracted rheumatic arthritis.

It seems likely that the high incidence of acute nephritis in this family following infection with type-1 streptococcus was at least partly due to a " nephritogenic " variant of type 1. This is suggested by the fact that the sera of the patients showed a more powerful bactericidal power against the strain of type-1 streptococcus, involved in this outbreak, than against a stock " non-nephritis " type-1 streptococcus.

Summary

Four cases of acute glomerulonephritis were detected in one family, following infections of the upper respiratory tract with β-hæmolytic streptococcus group A, type 1.

A distinct " nephritogenic " action has not previously been ascribed to the type-1 streptococcus.

We thank Dr. E. W. Skipper for permission to publish; Prof. C. H. Stuart-Harris and Dr. D. Verel for access to the notes of case 2; and the family practitioner, Dr. P. W. O'Brien, for helpful information. The streptococcal grouping was carried out in the departments of Dr. J. Colquhoun and Dr. E. H. Gillespie, to whom we are grateful for criticism and advice. We also thank Dr. R. E. O. Williams who kindly typed the organisms, demonstrated type-specific antibodies, and discussed the outbreak with us.

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Reviews of Books

Scottish Social Welfare, 1884–1914

THOMAS FERGUSON, C.B.E., M.D., F.R.C.P.E., professor of public health, University of Glasgow. Edinburgh: E. & S. Livingstone. 1958. Pp. 610. 42*s*.

THIS vast storehouse of information carries on the story begun in *The Dawn of Scottish Social Welfare*, published in 1948. If the later period differs from the earlier days in that its contrasts are less spectacular, the change which has overtaken social affairs since 1914 is still remarkable: and no less remarkable is the change which has come over the public attitude to social problems. Long and interesting chapters deal with general environment, housing, food, the relief of destitution, infectious diseases, the care of the sick, and the welfare of mothers and young people. Particularly interesting are the changes in such varied communities as the city of Glasgow and the isolated crofters in distant islands. In both places the housing problem was formidable and utterly different.

To begin with, the education of the adult population of remote parts, especially in the Hebrides, did not improve rapidly, so far at least as capacity to sign marriage registers was concerned. In Scotland as a whole, 10% of men and 20% of women signed by a mark in 1862 and 1872, and 7% and 14% respectively in 1881. Judged by this standard, much the most backward counties were Inverness and Ross and Cromarty; in Ross and Cromarty, 34% of men and 49% of women signed by the mark in 1862, 26% and 49% in 1872, and 24% and 47% in 1881. But the report of the Crofters' Commission in 1884 was able to claim that, while the educational level of adults in these counties was much below the Scottish average, the number of children being educated in that year was greater in proportion to population than in any other county except Caithness. By 1910 the figures had fallen to 5%.

Sekretionsstudien am Pankreas

Experimentelle und anatomische Pathologie. Dr. VOLKER BECKER, Pathologisches Institut der Universität Kiel. Stuttgart: Thieme. 1957. Pp. 119. DM 29·50.

Dr. Becker's monograph is a thorough attempt to correlate the histological features of the excretory tissue of the pancreas with the functional states produced in animal experiments. Thus, the static picture of a histological section is identified with a definite stage in the disease process. The results of ethionine-inhibited protein synthesis, of parasympathetic, splanchnic, and secretin stimulation, and of duct ligation, are described in laboratory animals killed at different intervals after the experiment began. And work has also been concerned with the size and shape of secretory cells, distribution of zymogen granules, basal basophilia (as an expression of ribonucleic-acid content), size of nuclei, and distribution of chromatin and of nucleoli.

Findings in human necropsy material are then described and interpreted on the basis of animal experiments. 350 cases were studied, in 50 of which the necropsy was performed less than two hours after death. Dyschylia, a secretion of abnormal fluid, and parachylia, an abnormal pathway of secretion, are terms used and discussed. Reasons are examined for the belief that the dual secretions—parasympathetic-stimulated, rich in enzymes (proteochylia), and secretin-stimulated, alkali-rich and aqueous (hydrochylia)—have their morphological equivalent in an anatomical partition, the first being secreted by cells of the acinus, the second by cells of the isthmus.

Some of Dr. Becker's claims may be contested. Thus, the increase in chlorides in the saliva in fibrocystic disease of the pancreas is explained by deficient dilution via duct cells; but the function of duct epithelium is water resorption against an osmotic gradient. The strong reduction of tetrazolium salts by the duct epithelium, so conspicuous in the parotid and submaxillary glands, is wrongly attributed to pancreatic ducts also. The role of postmortem autolysis is probably underestimated.

Anyone interested in pancreatic disease will find the book useful and stimulating, and there is an exhaustive list of references.

The Clinical Physiology of Physical Fitness and Rehabilitation

ERNEST JOKL, M.D., professor and medical director, Rehabilitation Center, University of Kentucky. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958. Pp. 194. 63*s*.

THIS book is based on an essay for which the author was awarded the Buckston Browne prize and medal of the Harveian Society of London. He suggests that, though medicine has made great advances in the past fifty years, these have been accomplished principally by utilising laboratory and experimental methods, to the detriment of the art of clinical observation. In the present work he seeks to redress the balance, pointing out that the worker in physical medicine and rehabilitation is ideally placed to develop new clinical techniques.

One obstacle is that the scientific basis of rehabilitation is still only vaguely defined. Indeed, the realisation that rest alone will not always suffice for the optimum recovery of the body from a disease process, is comparatively recent. Dr. Jokl elaborates the thesis of Julius Cohnheim and William H. Welch that "the healing power of nature is frequently incomplete and imperfect" by describing instances in which dissatisfaction at the results yielded by this natural power, operating alone, led to high and imaginative standards in rehabilitation. Such standards have sometimes resulted in almost incredible accomplishments (for example, the world record in hammer-throwing was, in 1956, held by a man whose left arm was almost totally paralysed).

This book can profitably be examined from several different angles. It is a monograph in physiological research, reporting original work on the prognostic significance of the ballisto-cardiogram. It is a study of the recent history of physiology, embodying a series of short, but attractively illustrated, biographies of such figures as Sir Charles Bell, Hughlings Jackson, and Amand Duchenne. Finally, the case-histories it embodies constitute intriguing and stimulating examples of the remarkable standards of recovery which are, on occasion, attainable even by the seriously handicapped.

An Atlas Concerning Morphological Aspects of Visceral Nerve Endings

Contribution to the Study of the Problem of Interoceptors. Prof. Dr. I. NICULESCU, M.D., corresponding member of the Rumanian Academy of Sciences. Bucharest: Editura Medicala. 1958. Pp. 455.

THIS work appeared some months after the death of its distinguished author. The text amounts to only 30 pages, but it is repeated in several languages, including English. It includes a useful section on the intraneuraxial pathways of the interoceptors and proprioceptors, and a short account of the cortical representation of vegetative functions. The many drawings illustrating nerve-endings in various laboratory animals are mostly in two or three colours and are very clear. Methylene-blue and carmine appears to be his method of choice for fresh impregnation, but use is also made of various standard silver techniques. One illustration shows the autonomic microganglia of the subserous layer of the human fœtal bladder, which is so rich in synaptic structures.

Eden and Holland's Manual of Obstetrics (11th ed. London: J. & A. Churchill. 1957. Pp. 751. 63*s*.).—In the latest edition of this classic Mr. Alan Brews provides a comprehensive and easily read account of current obstetric practice. It is profusely illustrated with excellent diagrams and plates. There is little emphasis on manipulative and operative obstetrics, which is proper in a book intended primarily for the undergraduate. In spite of claims to the contrary the M.R.C.O.G. candidate will be obliged to read more widely: obstetric anæsthesia is only briefly considered, Kielland forceps get half a page, pudendal-nerve block is just mentioned, Lovset's manœuvre is not described, and the account of the management of breech delivery is not fully up to date. Nevertheless, the book can be thoroughly recommended to the undergraduate, and the general practitioner will find in it a sound answer to every unusual obstetric problem.

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Resources for Research

THOSE who visit American medical schools are impressed by the amount of money at their disposal for medical research. Last year the grant from Federal funds alone was $186 million; industry contributed $90 million; charitable foundations earmarked $35 million for specific projects; and further substantial sums came from local collections (e.g., "Heart Sunday") and sums allotted by individual States to their universities. The municipality of New York has just set up its own Health Research Council with an initial appropriation of $600,000 and a possible eventual budget of $8 million a year (see p. 702). Congress has now been told by a special committee that it is not putting enough money into medical research and that $1000 million annually should be spent by 1970.[1] Yet already Congress is putting into research twenty times the budget of our Medical Research Council. This vast endeavour is exemplified in the National Institutes of Health at Bethesda with 6000 medical and ancillary staff. In the U.S.A. all avenues into medical research are wide open, and there are splendid facilities even at the student stage. Hospital consultant staffs are far larger than ours, and at every grade each member is expected to contribute actively to the development of ideas in medicine. Dr. SMYTHIES' article on p. 689 of this issue graphically underlines the prominence of research in American thought. In our more strictly selective system, necessitated by relative poverty of money and facilities, many American investigators would hardly have had a chance. By full deployment of their talent, and by the efforts of great numbers, an immensely rich soil is being developed from which new research ideas can be harvested.

When new scientific approaches originate in this country they may be elaborated all too slowly by "one man and a boy" working in cramped space with makeshift equipment, whereas in the United States large teams at once get to work on every promising idea. Consequently we have depended on the United States for the development of new antibiotics; and to the United States, too, must go full credit for most of the progress in protection against poliomyelitis. These are advances well known to the man in the street, but far more important is the ferment of new biological ideas from which other discoveries will spring. Fundamental biological and physiological science in the U.S.A. is closely integrated with clinical research, and extensive laboratories are available not only to the basic medical scientists but also to clinicians for studying problems arising out of human disease. By contrast, medical research in this country is undergoing relative attrition despite an expanding economy. In the universities new building for medical and biological sciences is much more restricted than that for physical and technological subjects. There is no surgical animal research laboratory in any English university—though one is now nearing completion. There have been no new teaching hospitals in this country since the 1939–45 war; so even the application of the new methods developed here or elsewhere is frustrated or difficult. Careers in basic medical science have become unattractive in salary and prospects compared to the glamour of consultant medicine—once achieved. The young clinical trainee who engages in research is often terrified that he will thereby become labelled a "laboratory man" (derogatory only in this country) or too specialised for the next vacancy in a provincial hospital. The real gravity of our situation is underlined by the fact that some of our research directors and medical professors, as well as promising younger investigators, are leaving this country to work on the other side of the Atlantic, where they find that, in their laboratory and investigative work, they are given encouragement, lavish support, and almost unlimited opportunity. This is happening even though adaptation to the American way of life may be none too easy for the expatriate of mature years.

We may claim that, because of the very restriction of opportunities, there is a more concentrated selection of ability in British medicine—that in American medical research, as in the American economy, there is much waste. Our professional leaders are in fact very highly selected, but if the scientific training of our young men continues to be discouraged our leaders will be selected from a dwindling field of applicants. Already our medical faculties often find great difficulty in filling their professorial chairs. We justly pride ourselves that under the N.H.S. there are more specialists than ever before; but we should not pretend that this growth in specialist services will by itself keep British medicine in the forefront. We cannot maintain our standards without the vigorous pursuit of research in our medical schools, for even good routine will decline without the stimulus of critical thought engendered by investigative work. Scholarship alone—meaning the study of other people's thoughts—can never keep a profession alive. It failed in the Middle Ages and it would fail again now.

With our smaller population and national income we naturally cannot spend as much money on research as the United States. But we could with advantage spend more than we do, and we should make sure that our resources are used with imagination. Poverty need not make us too despondent, or proud, to learn from the American system such useful lessons as the encouragement of research among all branches of the profession, including students. The clinical prizes offered by some regional hospital boards and the more ambitious studies being made by the College of General Practitioners recognise this need. Again, though we cannot compete with the generosity of American industry and trusts, we could perhaps foster a new age of patronage. Lord Nuffield has already shown us the way; two of the

1. *N.Y. Times*, July 14, 1958.

royal colleges have lately received princely gifts for research; and the Mental Health Research Fund, which supports some investigations into the problems Dr. SMYTHIES mentions, offers an opportunity for ordinary citizens to make small contributions.

Our Commonwealth links no longer depend on the strength of our military force, but on our scientific, cultural, and commercial leadership. (Many of us can remember the uplift to the national pride and prestige of Canada which followed the discovery of insulin.) Supported by the basic disciplines of physiology, biochemistry, and microbiology, which in turn utilise techniques of physics and chemistry, medical science is a part of general science. Progress in one science inevitably impinges on all associated branches. Uneven progress of science is impossible, and thus the present policy of preferential development of the physical sciences seems to be utterly faulty. In the U.S.S.R., where the academician holds the highest place in society, there are signs of an intensified application of basic sciences to medical problems. In this country we have no lack of talent; but without more financial encouragement, more laboratories, and more facilities for research, we shall lose our best workers, and gradually the standards of medicine even at a practical level will decline.

First Responses to Local Infection

How primary bacterial infections may in nature be limited to the site in which the organisms first lodge and multiply is still unknown. Although hyperæmia, heat, swelling, suppuration, and healing follow primary infections and are known to be due in sequence to to dilatation of blood-vessels, increased blood-flow, œdema, and diapedesis of leucocytes, then regression of these dynamic events, and finally scarring, their relation in time to the death and restricted spread of bacteria is still open to question. Direct visual observations of these events in response to injury in transparent tissues have usually been made using chemical or physical agents with limited action whose extent depends on the dose. Yet even with these it cannot be judged when the stimulus to the response ends and the consequences of the response begin. The problem of these time-sequences is increased with living micro-organisms through their own capacity to multiply and produce injurious substances which in their turn damage the tissues chemically. Thus an infection with living bacteria will be limited and localised only if the bacteria are prevented from escaping and are killed on the spot. On the spot or nearby are phagocytes and their potential progenitors which can kill bacteria; and destructive antibody may be generated locally and possibly rapidly. In vascular tissues both cellular and humoral antagonists are brought to the site by the blood-stream. Though the possibility of local destruction of bacteria in non-vascular regions has long been known, it has usually been assumed that blood-borne phagocytes and non-specific immune substances are decisive in limiting infection in vascular tissues. Localisation has been attributed by some to thrombotic plugs in efferent blood and lymphatic vessels. The decisive factors limiting infection will be those which first kill infecting bacteria. Thus the time after infection at which these are all dead or so greatly decreased as to be ineffective must first be known before the manner of their death can be determined. A decision to investigate local events in the first five hours after the infections which were known to remain localised was arrived at by BURKE and MILES [1] on the basis of much previous experience of MILES and his coworkers [2-4] using enhancement of infectivity to judge the time when most of the bacteria were killed.

Inflammatory lesions of a standard size were obtained consistently at twenty-four hours after injections of suspensions of known bacterial content. To produce a final lesion of the same size different numbers of bacterial cells were required for different micro-organisms. Experience showed that the size of the definitive lesion could be modified much by various enhancing agents. When these were injected within three to four hours after primary infection the size of the twenty-four-hour lesion was increased. The enhancing agents were adrenaline, general shock, and liquoid (an inhibitor of complement). The degree of enhancement was measured as increase in lesion size, and it could be interpreted as equivalent and proportional to an increase in the number of bacteria of the primary infection. Enhancement occurred, however, only when attempted within three to four hours after primary infection. From these observations it was concluded that after the first few hours the bacteria were either dead or so greatly diminished as to be incapable of responding by further damaging action to the favourable conditions afforded by enhancers. The death-rate of bacteria was estimated at 50–99·9% in the first two hours of infection. In a further paper MILES and MILES [5] have described a method of making bacterial counts in fresh tissues.

Having found a decisive period within which both lesion size and localisation were determined for a given dose, BURKE and MILES [1] investigated the sequence of events in early infective inflammation. Increased permeability (measured by dyeing with intravenous pontamine sky blue), increased stickiness of capillary endothelium (demonstrated with intravenous saccharated iron oxide), and tissue leucocytosis (estimated in stained sections) were used as criteria and measures of inflammatory response. Capillary dilatation and œdema are not amenable to accurate measurement, though both are more directly representative of response. Nine different infective agents, including one, *Streptococcus pyogenes*, isolated from a natural guineapig infection, were used to obtain lesions of a standard size of 10 mm. in twenty-four hours. In 6 of these the time-relations of vascular reactions were similar. In the first two hours of the decisive period macroscopic signs of inflammation were scanty; they did not

1. Burke, J. F., Miles, A. A. *J. Path. Bact.* 1958, **76**, 1.
2. Evans, D. G., Miles, A. A., Niven, J. S. F. *Brit. J. exp. Path.* 1948, **29**, 20.
3. Miles, A. A., Niven, J. S. F. *ibid.* 1950, **31**, 73.
4. Miles, A. A., Miles, E., Burke, J. *ibid.* 1957, **38**, 79.
5. Miles, A. A., Miles, E. *J. Path. Bact.* 1958, **76**, 21.

become obvious until the third or fourth hour; and they were not fully developed for several hours. Capillary permeability, measured by the extent and depth of staining in the region around injected bacteria, increased transiently in the first half-hour, and subsequently there was a larger increase with a maximum at three to four hours. In this second phase œdema and microscopically detectable leucocytosis increased. Yet later, after the fifth hour, when induration and leucocytosis continued to increase, there was low permeability to the dye. This observation causes BURKE and MILES to suggest that the relation of vascular permeability phenomena to effective defence against local infection should be re-examined. Of all the terms used, induration is left least defined. If there is indeed "hardening", this is more than simple œdema. In a previous publication MILES et al.[4] stated that no fibrin could be demonstrated outside the central area which was destined to undergo coagulation necrosis. Thus it seems that only the accumulation of phagocytes can account for this change in texture. Great insight into the manner of dye diffusion along fibres and into œdema fluid has been provided by MCMASTER and PARSONS [6] Their methods of observation may help to explain why dye no longer escapes while œdema fluid and leucocytes collect and the whole lesion becomes hardened. During this early period there was no evidence of thrombosis of blood or lymphatic vessels.

To what extent can these findings be applied to natural infection? In the experimental infections the pathogenicity of the microorganisms used might be questioned; and BURKE and MILES imply, and in one instance MILES and MILES [5] state, that with larger bacterial doses spreading and generalised infections occurred even in the absence of enhancers. The particular example of systemic infection was seen with *Str. pyogenes* [7 8] which had been isolated from a natural guineapig infection. This essential piece of evidence removes two further objections to the realism of the experiments. All the organisms, including the streptococci, had been frozen, dried, stored, and washed with distilled water before use. Several million were injected to represent an infecting dose, and they were introduced intradermally in a stabilising suspension which formed a small bleb about 1 mm. in diameter. How the suspension compares quantitatively with natural infection might be estimated. Conditions inside a bleb are described, and further information on the situation may be gained from the revealing observations of S. H. BENSLEY.[9]

The many observations now assembled indicate that the decisive period in which infection is limited precedes the classical early signs of acute inflammation in vascular tissues, and suggest that these early signs are responses to the aftermath of infection. The versatility displayed in this series of publication should enable those taking part to proceed to the even more difficult task of detecting early unseen agents of bacterial destruction.

6. McMaster, P. D., Parsons, R. J. *J. exp. Med.* 1939, **69**, 247, 265.
7. Miles, A. A. *in* Lectures on the Scientific Basis of Medicine; vol. 3, p. 235. London, 1955.
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9. Bensley, S. H. *Anat. Rec.* 1934, **60**, 93.

Papa Virchow

As part of its autumn meeting in London, the Association of Clinical Pathologists is celebrating on Oct. 3 the centenary of the publication of VIRCHOW's *Die Cellularpathologie* with a symposium on the pathology of the cell, to be opened by Sir ROY CAMERON with a paper briefly entitled "1858". It is an event well worth celebrating.

Modern biology, after some centuries of irregular acceleration and many false starts, may fairly be claimed to have been launched on its tumultuous career with the publication in three successive years of three of the most seminal works of the whole scientific canon—PASTEUR's *Mémoire sur la fermentation appelée lactique* in 1857, *Die Cellularpathologie* in 1858, and *The Origin of Species* in 1859. It is easy to think of VIRCHOW's work as important only as the well-head (with MORGAGNI's *De Sedibus*) of pathology, but it is a great deal more than that. It established the cell as—after the body-as-a-whole—the prime unit of investigation, not only for medicine, but for biology in general. Cells were of course not invented by VIRCHOW. The word is as old as HOOKE's pioneer microscopic description of cork in 1665. The idea that living matter is characteristically divided into separate units, each with a nucleus, stemmed largely from the work twenty years earlier of SCHLEIDEN, SCHWANN, and MÜLLER, and, in the descriptive sense at least, had already been greatly developed by KÖLLIKER and REMAK. But VIRCHOW added two major contributions to the "cell-theory". In the first place, he is responsible for one of the great biological generalisations—*Omnis cellula e cellule*. By something more than coincidence, the core of all three of these near-contemporaneous works is their demonstration, on three very different planes, of the continuity of living matter. DARWIN destroyed separate creation, and showed that all species stem from a single family tree; PASTEUR destroyed spontaneous generation, and showed that his "ferments", which were microorganisms, came from pre-existing living matter; VIRCHOW destroyed the idea that cells were a mere local crystallisation of protoplasm from an undifferentiated continuum, and showed that every cell resulted from the division of another cell. In the second place VIRCHOW established the "cell-theory" by showing that it had practical use. The sharp realities of medical practice afford the sternest test and, if successful, the most brilliant vindication of any biological theory. The cell-theory made it possible to understand the appearances presented by diseased tissues under the microscope, and added a new dimension to pathology (some day the electron-microscope will find its VIRCHOW: it is still in the HOOKE stage). Though his techniques for the preparation of sections were primitive —paraffin embedding and most of our standard stains were at least a decade away—he launched the science of histopathology. The enormous increase in accuracy of prognosis possible (in the case of tumours especially) by the use of microscopic methods based on VIRCHOW's ideas supplied the best possible proof of their validity.

It is sad that most have heard of VIRCHOW as a diagnostic histopathologist only in the matter of the Emperor FREDERICK III; his misdiagnosis as benign of the biopsy taken by MORELL MACKENZIE from the Emperor's laryngeal carcinoma was one of the more distressing factors in that most distressing case. Yet we may remember that even today this can be a difficult diagnosis, and that MACKENZIE, working with a mirror and no anæsthetic, may well have missed the real tumour. Moreover, though it ruined MACKENZIE, the mistake was probably for the good of the patient, who would have been subjected otherwise to a laryngectomy, the mortality of which at the time was at least 75%. In any case, before *Die Cellularpathologie* there would have been no biopsy. VIRCHOW in fact made many mistakes. Beside his brilliant elucidation of the cellular nature of leukæmia and of sarcoma there stands, for instance, a detailed account of the origin of carcinoma from the cells lining lymphatic channels. But it is for his achievements rather than his mistakes that he is to be remembered. And they were innumerable. For fifty years he was the leading figure in German pathology, and this was a time when German pathology far outstripped that of the rest of the world. He was in addition very many other things—anthropologist, archæologist, hygienist, politician. His famous *Archiv*, founded in 1847 when he was 26, and still one of the world's leading medical journals, contains in its earlier volumes many contributions on subjects far removed from pathology.

He remains even today the father figure of pathologists the world over. He established the microscope as an essential tool of medical research and of medical practice. He established pathology as an independent discipline, occupying the vantage point of a middle ground between the ivory tower of pure science and the clinical hurly-burly of pure application. If today the average pathologist seems to have rather diverse interests, concerning himself with the blood-groups of the Aztecs one month and the hospital drains the next, he—and with him the whole profession and its patients—owes more than he generally realises to the example of Papa VIRCHOW.

Annotations

LAYMAN'S AID

FOR eighty years the Order of St. John of Jerusalem, through its Ambulance Association, has produced manuals for the instruction of the layman in the immediate management of injuries and sudden illness. For almost as long the St. Andrew's Ambulance Association and the British Red Cross Society have had similar textbooks. This year their common aims and practices have had their obvious consummation in the production of a joint manual, simply titled *First Aid*.[1] Nearly all accidents and sudden illnesses are seen and treated first by a layman, and people keen to help their fellows turn to accidents and illnesses as an obvious opportunity to serve. Policemen, firemen, railwaymen, and pitmen, engaged in hazardous work, voluntary institutions whose members attend public meetings, young men and women who climb mountains or fly, and indeed anyone who takes his car out of the garage, may be the first to see someone suffer injury, or may suffer one himself. The doctor who tries to repair the damage often appears late in the succession of those who have contributed in some way to its treatment.

It is part of the system of training first-aiders that advice shall be simple, clear, and dogmatic. Hesitancies must be suppressed, and every dilemma must be resolved before instructions on first-aid are laid down. This book will be the ultimate authority for many people for many years to come.

The first and perhaps the greatest dilemma facing the authors of such a book is between simplicity and comprehensiveness. A simple manual reaches a wider public, and, because first-aid is needed widely, some would say the barest minimum of information will do the greatest good. This argument influenced the Priory of Canada when they published *Fundamentals of First Aid*[2] three years ago. In this book Dr. Robert A. Mustard discarded all discussion of shock, and all description of pressure-points. He condemned the tourniquet outright as a first-aid instrument, discouraged the use of bandages to stabilise fractures of collar-bone, jaw, ribs, pelvis, and some others, and in many other ways shortened the course and limited the exercises which have been practised throughout this country for generations. Our own book, on the contrary, contains more material than it did thirty years ago, although its size, because of streamlining and simplification, is not much increased. It prefers comprehensiveness, encourages the maintenance of a corps d'élite, aims particularly at the team which trains diligently, and fosters the cult of first-aid training by devoting, for instance, eighteen pages to stretcher exercises.

Yet in many ways this new book brings the practice much closer to modern conditions. Although sections on civil defence and labelling of casualties in war might indicate that it is becoming more complicated, the improvement in communications, hospital services, and medical care make the first-aider's task easier under our present organisation. Elaborate splinting of fractures may not be necessary if a hospital is near, and we are warned not to delay disposal of a casualty by work which is to be undone a few minutes later. Experts in first-aid will still argue over occasional details. Holger-Neilsen takes definite priority over Schafer in artificial respiration, though both methods are well described. We are still to transport the patient with a fractured spine on his back, though an appendix instructs on the prone position " if it is unavoidable ". Every casualty officer will have sympathy with the first-aider who is being coached in differentiation between twelve or more listed causes of unconsciousness.

Dr. L. S. Potter's editing has had much excellent writing to draw on from previous editions, but we detect a new and vivid pen in places: " the whole spine is *strapped together* [our italics] by bands of strong fibrous tissue ". Every medical student might well prepare himself for more detailed studies by reading the simple survey of human anatomy and physiology at the beginning. This work is, of course, not intended primarily for doctors, though no doctor would lose by studying it. Many

1. First Aid: the authorised manual of the St. John Ambulance Association, the St. Andrew's Ambulance Association, and The British Red Cross Society. 1958. 4s.
2. Fundamentals of First Aid. By Robert A. Mustard. Published and approved by the Priory of Canada of the Order of St. John, 1955.

thousands serve the ends to which doctors are dedicated, and it is here to serve them. The ancient Hospitallers of St. John and their kindred brotherhood the Templars (whose seal showed two knights upon one horse) would have approved this combination of forces in a single vehicle, in pursuit of a single aim.

THE COMMON COLD

IN this coming season of mists and mellow fruitfulness our thoughts turn once more to influenza and the common cold. After last year's bumper harvest the influenza virus may decide that the soil is too heavily immunised. But that hardy old perennial, the common cold, is unlikely to give us any peace; and as the schools open, we can expect it back again.

Dingle [1] gives us a timely reminder of our ignorance of the subject in his presidential address to the American Association of Immunologists. In a group studied by Hope-Simpson,[2] each person has on average 7 colds a year, and therefore spends practically one day out of every five coughing and sneezing. Many of us will react to this by protesting that we hardly ever catch cold, and we will support this by describing our favourite prophylactic or remedy. If so, we shall be doing just what Dingle says we shall do, because ignorance of the cause, predisposing factors, and treatment of the common cold is so great that the field is wide open for theories and unproven assertions. One of the commonest—that colds are caused by chilling—is beginning to weaken under constant experimental attack, and it now seems clear that a feeling of chilliness is often an early symptom of infection rather than a causal or predisposing factor. But it may take some decades before the public are persuaded of this. Dingle also emphasises our ignorance of the methods of natural transmission of colds and of factors of resistance and susceptibility. Psychological factors in resistance to colds are now being invoked; and, if this seems an unlikely association to some, it is worth reflecting that Dingle was himself responsible for a most careful trial from which it emerged that, three weeks after having been infected with a common-cold filtrate, volunteers showed no specific immunity to the same virus. Attack-rates are higher in children and tend to decrease with age, but it is not yet established whether this reflects increasing immunity or diminishing exposure to virus.

If the disease is full of puzzles, the virology, according to Andrewes in a De Lemar lecture,[3] is not without its problems. New techniques of virus isolation and study continue to reveal more and more viruses, and often the biological characters of the virus are known in some detail before its epidemiological significance is understood. Besides the influenza viruses and adenoviruses, new viruses are being recovered every few months from people with upper-respiratory disease of one kind or another. The question arises whether new pathogens are being discovered, or whether we are just beginning to amass a collection of relatively harmless virus commensals which correspond to the bacterial commensals isolated in the first flush of enthusiasm for detailed bacteriological investigations. So far none of the viruses isolated has shown a clear association with common colds, but Andrewes nevertheless raises the question whether the common cold will be found to be a fairly common response to infection with a large number of different viruses, or alternatively where there is a single common-cold virus. Until now, attempts at continuous cultivation of it (or them) in the laboratory have not proved successful. In this phase of rapid advances it will be surprising if the common-cold virus resists cultivation for very much longer—although, even if the virus gives in quite soon, we may still spend many years wearing our flannel underwear to keep off chills. Meanwhile it is noteworthy that Dr. J. Morrison Ritchie, whose latest report appears on p. 699 of this issue, has confirmed his earlier observation that full development of a cold can often be prevented by administration of an antibiotic at the onset.

1. Dingle, J. H. *J. Immunol.* 1958, **81**, 91.
2. Hope-Simpson, R. E. *Proc. R. Soc. Med.* 1958, **51**, 267.
3. Andrewes, C. H. *Bull. Johns Hopk. Hosp.* 1958, **103**, 1.

POSTNECROTIC CIRRHOSIS

EVER since 1895, when Marchand [1] first described the development of nodular hyperplasia of the liver after an attack of acute yellow atrophy, the relation of this nodular lesion to other forms of cirrhosis has been disputed. Lichtman [2] has been outstanding among those who refuse to regard it as an example of true hepatic cirrhosis, on the grounds that progressive replacement of parenchymal cells by scar tissue is the essence of true cirrhosis and the nodular hyperplasia that follows massive hepatic necrosis seems to represent the static end-result of a single acute episode. On the other hand, Mallory,[3] Karsner,[4] and many others have long regarded nodular hyperplasia as a true cirrhosis, to which the term postnecrotic cirrhosis is usually applied. Delay in resolving this difference of opinion has been due to many factors, but principally to the relative rarity of the condition and to our ignorance of the ætiology of almost all forms of hepatic cirrhosis. Now a study by MacDonald and Mallory [5] of the 221 cases of postnecrotic cirrhosis that came to necropsy at the Boston City Hospital between 1917 and 1956 has provided convincing evidence that the disease is progressive.

Unfortunately, this study throws little fresh light on ætiology. Exposure to known liver poisons was negligible. Malnutrition apparently played only a minor role, since nutrition could be regarded as adequate in over half the patients; but in 41% chronic alcoholism was a feature. The outstanding result of the analysis of the case-records was the possible association with virus hepatitis. No less than 24% gave a history of a previous attack of hepatitis or jaundice, and a further 44% had received multiple parenteral injections for one reason or another, thus exposing themselves to the risk of homologous-serum hepatitis. But even in the former group, in only a third of the patients was the relation of the cirrhosis to the clinical attack of hepatitis reasonably direct. In the other two-thirds there was an average interval of over fifteen years between the earlier attacks of jaundice and the appearance of symptoms unequivocally associated with cirrhosis. The only justifiable conclusion from these data is that viral hepatitis is the most likely agent responsible for the majority of cases of postnecrotic cirrhosis; and the undoubted increase in incidence of this type of cirrhosis in recent years harmonises with this conclusion. Yet it is not easy to understand why clinical manifestations of cirrhosis appear so long after the hepatitis. Possibly the virus persists through the intervening years, causing slowly progressive damage that eventually emerges above the clinical threshold with hæmatemesis or ascites, or

1. Marchand, F. *Ziegler's Beitr. path. Anat.* 1895, **17**, 206.
2. Lichtman, S. S. Diseases of the Liver, Gallbladder and Bile Ducts; vol. 1. Philadelphia, 1953.
3. Mallory, F. B. *New Engl. J. Med.* 1932, **206**, 1231.
4. Karsner, H. T. *Amer. J. clin. Path.* 1943, **13**, 569.
5. MacDonald, R. A., Mallory, G. K. *Amer. J. Med.* 1958, **24**, 334.

else the virus persists for months or years without producing any damage until, owing to some change in host-virus relationship, progressive necrosis of the infected liver cells occurs and leads to progressive cirrhosis. A third possibility has been suggested: if the initial damage produced were severe enough the resultant scarring might lead to vascular disturbances within the liver and thus to further necrosis and scarring. Glynn [6] suggested a similar sequence to explain the irreversible stage of cirrhosis in rats that have received twice-weekly injections of carbon tetrachloride.[7]

The ætiology and pathogenesis of postnecrotic cirrhosis are still far from clear. As MacDonald and Mallory point out, the main impediment is the failure at present to reproduce virus hepatitis in an animal other than man. Success here could lead to rapid progress in our understanding of postnecrotic cirrhosis.

CHORIONCARCINOMA: AN IMMUNOLOGICAL APPROACH

BECAUSE the immune processes in the causation of hæmolytic disease of the newborn have been determined, it is now possible to await its occurrence with some confidence and to set in motion the necessary treatment at the moment of choice. Just under two years ago it was shown that Hashimoto's disease of the thyroid gland was caused by a cellular antibody reaction to leakage of thyroglobulin out of the thyroid acini.[8]

This year a first attempt has been made [9] to apply the knowledge gained by P. B. Medawar and his associates in relation to tissue immunisation to the treatment of chorioncarcinoma. Even though the degree of success in this particular patient is hardly capable of scientific interpretation, because many additional treatments were employed, the ideas which underlay the attempt can be applied to other patients and could lead to a revolution in approach to this dramatic and distressing tumour.

The tissues of a mother and a child are not compatible; a skin graft from child to mother behaves as a homograft, not an autograft, because of the presence of paternal antigens in the cells of the graft. Since chorioncarcinoma originates from fœtal tissue, half the genes in its cells are derived from the father. Doniach et al. considered, therefore, that deliberate immunisation of a patient suffering from chorioncarcinoma by her husband's cells might induce or enhance her tissue incompatibility (homograft immunity) towards cells containing the husband's genes and might thereby check or even destroy the tumour. Immunisation was induced by intradermal or subcutaneous injection of white blood-cells from the husband on eleven occasions. The earliest injections produced an immediate local reaction which subsided within a week. The patient was tested by two means in an attempt to demonstrate tissue immunity to the husband's white blood-cells. Firstly, skin grafts were made from the patient, her husband, and another donor. The autograft survived but the two homografts disintegrated —the husband's more rapidly than the donor's. Secondly, leucoagglutinins were demonstrated to a titre of 1 in 64 against the husband's white blood-cells. These facts were regarded as evidence that immunity had developed in the patient against her husband's cells.

During and after the period of immunisation and testing, the patient, who had had hysterectomy for proved chorioncarcinoma, developed vaginal recurrence and lung metastases, both of which were treated by deep X-ray therapy, with temporary improvement. When extension of the pulmonary metastases was observed, four courses of treatment with an anti-folic-acid preparation were instituted; subsequently the lung shadows disappeared, and the symptoms were dispelled. This was two years after the start of symptoms. Doniach et al. consider that immunity may have helped the action of the anti-folic-acid drug.

Theoretically, it is to be expected that the very presence in the mother's uterus of chorionic cells, half of whose genes are derived from the father, will normally evoke a maternal tissue immune reaction which might check or modify their growth. Possibly, when chorioncarcinoma develops and spreads, this mechanism is lacking or in some way modified. Where the tumour spreads and spontaneously regresses, as it does in some cases, immunity may develop late or some kind of blocking mechanism may operate temporarily. There are " infinite gradations of antigenic relations between the components of different tissues and different species ".[3] There is clearly scope for further experimental study of these relations in chorioncarcinoma.

DEFINING OVULATION-TIME

FROM America comes the suggestion that the time of ovulation can be simply and accurately pinpointed by the use of strips of tape or paper impregnated with the enzyme glucose oxidase, which, when placed against the cervix, will demonstrate by change of colour from yellow to green the increase in glucose content of cervical mucus known to occur at the time of ovulation. Some physicians require the patient to visit the office daily for several days about the time when ovulation is expected [10]: ' Tes Tape ' is applied to the mucus cascade and the colour change in the tape is noted. What happens, or should happen, when ovulation is imminent or has just occurred, is a change of colour to brilliant green and later to a darker green, indicating that coitus in the next 12 hours is likely to prove fruitful. Doyle [11] of Boston, thinks that the tes tape can equally well be applied by the patient herself, using a cylindrical cardboard tampon. The woman inserts one of these for a few minutes daily from the 8th to the 16th day of the cycle, and, unless she is colour-blind, can see when the colour changes to green. She and her husband can then take appropriate action according to whether they want conception to occur or not. Correlation of these colour changes with other ovulation indicators (shift in basal temperature, *Spinnbarkeit*, positive palm-leaf reaction, secretory change in endometrium) has been established. Doyle has gone further and has demonstrated by colpotomy and at laparotomy the presence of a recently ruptured follicle and the production of a similar green colouration of tes tape dipped in spilled follicular fluid recovered from the pelvic peritoneum.[12]

The efficacy of this new method of dating ovulation can be confirmed only by trials on many volunteers. If further experience shows it to be accurate it should prove of value not only in the treatment of infertility, but also to those who practise the rhythm method of birth control.

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Special Articles

A TRIPLET PREGNANCY WITH CRANIOPAGUS TWINS

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WE report some preliminary details of a case of craniopagus twins. Two features believed to be unique are that the mother gave birth to one single normal healthy baby at the same time as the conjoined twins and that one of the conjoined twins has had congenital hypertrophic pyloric stenosis. The last case known to have been born in England was described in *The Lancet* exactly thirty years ago by Cameron (1928).

Craniopagus twins are the rarest of all conjoined twins, estimated at 1 in every 2 to 4 million births by Robertson (1953), who analysed Tartuffi's figures. Of 117 conjoined twins 86 were joined anteriorly by the thorax (thoracopagus), 22 posteriorly in the sacral area (pygopagus), 7 caudally by the lower abomen (ischiopagus), and only 2 by the skull (craniopagus). The present case is the 42nd to be recorded in the available literature, but the 6th since 1949, which may reflect no more than the present age's greater ability to read and write.

The usual fate of these babies has been death, sometimes in the first week, nearly always by the end of the first year. One set, the first on record, 2 girls joined by the forehead born in Bierstadt in 1495 (Münster 1559), lived until the age of ten years, when one died. The dead partner was cut away and the second died shortly after.

In Cameron's case an emergency separation was attempted by Mr. L. Bromley on the twelfth day because one was obviously deteriorating, but both died during the operation. Cameron commented that if the intradural spaces communicate, attempts at separation are useless. Technical progress in neurosurgery, plastic surgery, and anæsthetics has altered the prognosis to some extent.

The first success was reported by Sugar and Grossman in 1953. One baby died one hour after separation, but the other survived and was developing well at eighteen months. Voris et al. (1957) reported successful separation with satisfactory condition of both twins at two years and four months. These three sets resemble in the photographs the set reported here, the main junction being between the parietal bones (c. parietalis). The most recent paper, by Baldwin and Dekaban (1958), concerns craniopagus twins joined mainly at the forehead (c. frontalis), a rarer type in which the actual area of the junction is smaller. The twins were successfully separated in 1956 and both were within the normal range on their first birthday.

Separation with survival of both of the twins can be successful only if sufficient tissue is present for two separate individuals. The smaller the area of fusion the better the outlook. The tissues involved are the brain which has been adequate and virtually separate in hitherto reported cases. The covering membranes, especially the dura mater, are usually deficient over some part of the fused area. The arteries are expected to be independent, but the exact state of affairs must be established by angiography. The most probable stumbling-block is large venous communication. Skin to cover the vertex can be prepared without great difficulty. The problem of the replacement of skull bones has not yet been solved. In only two cases so far reported have both of craniopagus twins survived (Voris et al. 1957, Baldwin and Dekaban 1958); in Sugar's case (Grossman et al. 1953), where there was a closer fusion, a common sagittal sinus made survival of both impossible, and from the description this case resembles the present one most closely.

Case-record

Obstetric History

The mother attended hospital for her fourth pregnancy after ten weeks' amenorrhœa. She was a healthy woman with a childhood history of scarlet fever, measles, and mumps; both she and her husband are of European descent. Her first pregnancy had resulted in an abortion. Two years later she was delivered by forceps at the forty-third week of pregnancy of a stillborn female infant weighing 3670 g. (8 lb. 1½ oz.); postmortem examination showed that the baby was normally formed but had died of a massive aspiration of meconium.

After a further two years she was admitted at term for a surgical induction of labour under general anæsthesia. As she was not in labour in forty-eight hours after rupture of the membranes, a lower-segment cæsarean section was performed by J. S. T., delivering a boy weighing 9 lb. 1½ oz. (4125 g.) in good condition.

When first seen in her fourth pregnancy she was a fit woman, aged 36 years, height 5 ft. 5 in. She had slight varicose veins of the right leg and a recent rash on her fingers which she attributed to a wasp sting. At every antenatal attendance the height of the uterine fundus was noted to be greater than the duration of the pregnancy warranted. When Mr. J. D. S. Flew examined her at eighteen to twenty weeks the uterus was the size of a thirty-week gestation. Radiographic studies revealed triplets (fig. 1) and are reported in detail below. At the thirty-first week the abdominal girth was 46 in., and at the thirty-third 48 in. Symptoms of pre-eclamptic toxæmia were present for the first time at thirty-five weeks: the blood-pressure was 145/90 mm. Hg and there was a trace of albumin in the urine and slight peripheral œdema, so that the patient was kept on strict bed rest. The next day these abnormal signs had disappeared.

During the morning of delivery there was a small but definite show of blood per vaginam. The membranes were intact. The patient was well, three fœtal hearts were heard, and there were no uterine contractions. It was decided to deliver by cæsarean section that day because of the previous history and the known presence of fœtal abnormality in a multiple pregnancy. Under general anæsthesia (thiopentone, suxamethonium, gallamine, and cyclopropane) a classical section was performed. The first baby was delivered by the breech at 6.45 P.M.; he cried at once and was in excellent condition. The second amniotic sac was opened and twin boys joined at the cranial vault were delivered simultaneously at

Fig. 1—Antenatal radiograph at the 35th week. Three fœtuses are present, two conjoined at the crowns of their skulls with good mandibular and facial development and apparently normal trunk development.

6.48 P.M. Both cried at once. None of the babies presented any resuscitation problem, but in all mucus was cleared from the air passages. Ergometrine 0·5 mg. was injected intravenously into the mother and the same dose directly into the uterine muscle after the delivery of the babies. The previous lower segment operation scar was palpated and estimated to be 3 mm. thick. The uterine cervix was dilated to the diameter of two fingers' breadth. Postoperative progress was uneventful except for pyrexia of 100°F on the first and third days.

The placenta (fig. 2) was an intimately fused organ with two amniotic sacs which did not communicate.

Antenatal Radiographic Studies

The first abdominal radiographic studies at the nineteenth week showed three fœtal spines, indicating the probability of triplets. That only two skulls were seen, indicated some fœtal anomaly, possibly anencephalus. At the 28th week the radiographs were interpreted as showing one normal fœtus and a twin with two separate trunks and a gross cranial fusion. At the 35th week immediately before delivery by cæsarean section craniopagus twins were clearly seen with two normal trunks and good mandibular and facial development. The third fœtus showed no abnormality (fig. 1).

The Triplets

The first baby (a male weighing 5 lb. $9^3/_4$ oz., 20 in. long, skull circumference $13^1/_2$ in.) has appeared completely normal throughout. He was successfully breast-fed and at twelve weeks weighed 13 lb. 12 oz.

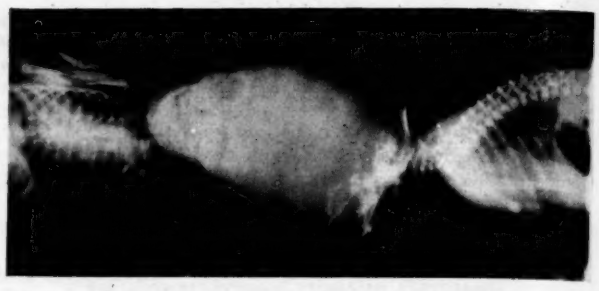
The craniopagus twins, also males, together weighed 9 lb. 12 oz. The vertices have virtually coalesced so that one skull cannot be moved on the other. They lie in a straight line, their long axes twisted through somewhat more than a right angle. This allows both to lie on the right or on the back while the face is turned half right. When on the left side the neck is strained and they are not comfortable.

General examination reveals no other abnormality. Rectal temperature readings differ and so do pulse and respiration rates, which do not synchronise. Simultaneous blood-pressure readings show 60 mm. Hg systolic in one and 50 mm. in the other. Both are blood-group O, rhesus positive: figures for Hb, white-cell count, and differential leucocyte count are not identical. Electrocardiograms differ in rate and pattern, both having a physiological degree of right preponderance. Electroencephalograms soon after birth, kindly carried out by Dr. G. Pampiglione, showed the brains to be separate.

Fig. 2—The placenta.

The twins are two distinct individuals with independent behaviour and personality. One may cry or feed while the other sleeps. One is bigger and stronger, but both are full of charm and mentally alert, and they do not appear to upset each other.

Clinical progress of the smaller twin has been interrupted by severe vomiting from eight to twelve weeks. Projectile vomit of curds with visible gastric peristalsis, and a palpable pyloric tumour, supported the diagnosis of congenital hypertrophic pyloric stenosis. Symptoms were relieved by a course of atropine methonitrate ('Pylostropin').



Figs. 3 and 4—Radiographs shortly after delivery, taken in two planes at right-angles. There is craniopagus with parietal fusion over a wide area. The long cranial axes of the two heads are approximately at right angles to one another. Facial bone formation of both appears perfect.

In radiographs of the conjoined skulls (figs. 3 and 4) no bony shelf can be seen between the vertices. Parietal fusion exists over a wide area. The long cranial axes of the two heads are approximately at right angles to each other. Facial bone formation of both appears perfect.

Discussion

Questions of ætiology are well discussed in some of the papers we have quoted, especially by Robertson (1953). We can only add that the presence of pyloric stenosis in one of the twins exemplifies the principle pointed out by Aird (1954) that conjoined twins "are seldom so precisely identical as separate monovular twins are". The future action in this case could not be better planned than in accordance with Aird's further statement that "however great the risk of the death of one or both children, it would seem that operation should nearly always be undertaken if the children are known each to have a full complement of the organs and tissues necessary for separate life".

In Cameron's case emergency operation failed, in Barbosa's (1949) both died three hours after operation, in Robertson's (1953) operation had to be abandoned. The three latest reports of partial or complete surgical success are quoted above. In this case great difficulty is likely to be encountered and the final separation will not be attempted before the first birthday. To achieve separation with the survival of both twins will require not only great prowess on the part of the surgeons but also sufficient tissues for two independent beings. To achieve one survivor will amply repay the great demands on the skill, the patience, and the emotions of all concerned. Fortunately it was possible to avoid publicity in this case for more than three months, giving the parents some time to recover from the immediate emotional shock.

Attempts to satisfy public curiosity about previous conjoined twins put a strain on parents, doctors, and

nurses. It is hoped that in this case newspapers and their representatives will exercise restraint and allow all those involved to conduct a hazardous undertaking in calm and peace. The authors (and the parents, with whom it has been discussed) feel that no photograph of the conjoined twins should under any circumstances be published during the lifetime of either twin.

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POST-HOSPITAL ADJUSTMENT OF CHRONIC MENTAL PATIENTS

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UNTIL recently, once a patient had stayed for two years continuously in a mental hospital, his chances of discharge were low (Kramer et al. 1955, Carstairs et al. 1955) and would become progressively lower until, by the eleventh year of stay, they would be about 1 in 100 (Registrar General 1955). This situation may now be changing.

The Royal Commission on the Law Relating to Mental Illness (1957) stated a new viewpoint:

"There is increasing medical emphasis on forms of treatment which can be given without bringing patients into hospital as in-patients or which make it possible to discharge them from hospital sooner than was usual in the past. It is not now generally considered in the best interests of patients who are fit to live in the general community that they should be in large or remote institutions such as the present mental or mental deficiency hospitals . . . No patient should be retained as a hospital in-patient when he has reached the stage at which he could return home if he had a reasonably good home to go to".

Brill and Patton (1957) and Kramer and Pollack (1958) show that in the United States in 1955–56, the year in which the use of tranquillising drugs became widespread in that country, the number of patients resident in State Mental hospitals declined, in reversal of a long-established trend. Brill and Patton showed that in New York State this could largely be ascribed to an increase in the number of discharges, especially affecting patients who had been more than two years in hospital. Neither Brill and Patton nor Kramer and Pollack (1958) indicated the level at which patients were functioning after their discharge from hospital.

Usually a psychotic patient discharged after a prolonged stay in hospital is not completely recovered but carries at least some residual disability. His remaining in the community will depend partly on the nature and degree of this psychiatric handicap and partly on the social environment to which he returns.

There have been many follow-up studies of former mental patients in general, and of patients with particular diagnoses or who have been exposed to particular forms of treatment (in most of which a stay in hospital of more than two years is claimed to carry a relatively unfavourable prognosis); but we have been able to trace only two studies which dealt specifically with the fate of long-stay patients after discharge from hospital:

Smith (1946) reports the outcome of 56 females who had been in hospital at least four years before discharge from St. Hans Hospital, Denmark. 54 of these still had symptoms; most required considerable help from social agencies. During the follow-up period (ranging from nine months to three years) 6 of these patients were readmitted and 1 committed suicide. Of the 49 who remained in the community only 6 were self-supporting.

Stringham (1952) reported the outcome of 33 patients discharged after an average stay in hospital of twelve years. 15 returned to hospital, but 6 of these were subsequently discharged again. Of the 24 still in the community about two years later only half were self-supporting. Stringham suggested that opposition on the part of the patient's family was the principal obstacle to their remaining in the community, and their ability to obtain gainful employment was the strongest positive factor in those who succeeded.

The present study was designed to ascertain the outcome of long-stay patients discharged from mental hospital and to look for factors in their history and in their subsequent social experiences which were associated with their level of adjustment in the community.

Method of Investigation

Selection of Cases

The population consisted of all those male patients who were discharged by any means from seven mental hospitals in or near London between July, 1949, and June, 1956, and who fulfilled the following criteria:

(1) Subjects of the United Kingdom by birth.
(2) Aged 20–65 on discharge.
(3) Had been in hospital two years or more before discharge.
(4) Not known to have gone to an address outside the Greater London Area.

Patients who died in the first year of discharge were excluded from the sample. There were 3 such deaths during the period, all of them natural. Patients who were out on trial for more than three months consecutively were included as from the end of the three-month period.

Selection of Informants

Whenever possible the primary informant was the housekeeper of the domestic group to which the patient went on leaving hospital—typically his mother, wife, or sibling, but in some cases his landlady. Any patient living alone was himself interviewed.

Follow-up Interview

An interview schedule was prepared covering 160 items, selected on the assumption that they might have a bearing on the patient's outcome. The schedule was usually completed for each patient after a study of the hospital case-notes and an interview with the primary informant lasting an hour to an hour and a half. Sometimes more than one person was interviewed.

The conduct of the interview was not formalised, but interviewers used a check-list to ensure that all the items had been covered. Each of us took part in interviewing, with weekly meetings for discussion of possible ambiguities in the recording of particular items; in this way it was hoped to ensure uniformity in the recording of data from the interview.

Measures of Outcome

For the purpose of analysis each patient's outcome was assessed in terms of the following criteria:

(1) *Duration of discharge period.*—"Success" (S) was defined arbitrarily as staying out of hospital for at least a year; readmission for more than a month in the year following discharge was counted as "failure" (F). This criterion of success proved to be relevant, especially for schizophrenia. Since information was obtained at intervals of one to six years after discharge, it was possible to calculate that, of the patients who relapsed during the six years, 74% of the schizophrenics and 58% of the non-schizophrenics did so within the first year.

(2) *Level of social adjustment.*—All patients counted as successes were rated by a scale of social adjustment, in which 1 point was given for each of the following three items: (*a*) being gainfully employed for five of the last six months in the first year of discharge; (*b*) being able to look after himself as regards appearance, dress, and use of money; and (*c*) showing adequate interpersonal relationships—i.e., without gross disturbances such as violence, paranoid ideas, or extreme withdrawal.

A score of 3 points rated "full adjustment"; 2 points "partial adjustment"; and 1 or 0 points "poor adjustment".

Some Characteristics of Population Studied

From the records of the seven hospitals 240 men were identified who fulfilled the necessary criteria, and schedules were completed for 229 (95%). Follow-up information could not be obtained for 11 of the original population, of whom 9 were diagnosed as schizophrenic, 1 as depressive, and 1 as psychopathic. A search of the records of the Board of Control did not reveal evidence that any of these 11 patients had been readmitted to mental hospitals since discharge; all have been omitted from our analysis.

Diagnoses

The diagnoses of the population studied were as follows:

	No. of cases
Schizophrenia	156
Depression	26
Epilepsy	18
Organic psychoses	10
Psychoneuroses	9
Mania	5
Other	5
Total	229

If the population is then divided into two main categories "schizophrenia" and "other" it can be further described in terms of the following factors:

Age.—The mean age of schizophrenics was 39·4 and of those with other diagnoses 45·0; in both the age range was 20–65.

Length of stay.—The two main categories of diagnosis had comparable lengths of stay for the admission to hospital which preceded this discharge, with a mean of 6·5 years (range 2–30 years).

First admissions.—31·4% of schizophrenics and 43·8% of those with other diagnoses were first admissions.

Marital status on admission.—77·6% of the schizophrenics and 42·5% of the others were single on admission.

Patients' Condition on Discharge

Before assessing the patients' outcome one would like to know as accurately as possible their mental state at the time of discharge; but in this retrospective study precise information on this point was unavailable. Some measure of the patients' mental state was, however, provided by the following observations:

(1) *Whether discharged on or against medical advice.*—31% of schizophrenics and 15% of the others were discharged against advice.

(2) *Whether recorded as recovered, relieved, or not improved on discharge.*—Of the schizophrenics 14% were discharged as recovered, 65% as relieved, and 21% as not improved; for the other patients the proportions were 13% recovered, 77% relieved, and 10% not improved.

(3) *A rating of the patients' level of disturbance of behaviour* while living in the community a year after discharge or just before readmission in the case of failures.—This was estimated on the basis of questions about ten specific features of the patient's behaviour and was rated in three categories. Patients who showed only minor peculiarities, or none, were rated "nearly normal". Patients with evident peculiarities which did not, however, preclude their moving about in society were rated "moderately disturbed" (e.g., a patient with hallucinations and paranoid ideas who found a succession of jobs only to quit them abruptly in response to his delusions). Patients showing more severe disturbances of behaviour, such as could be cited in recommending certification and interfered seriously with his social life, were rated "severely disturbed". It will be appreciated that this rating made at a later date can only give a somewhat conjectural (but still useful) indication of the patient's condition on discharge.

Of the schizophrenic patients 39% were rated nearly normal, 35% moderately disturbed, and 26% severely disturbed; of the remainder 45% were rated nearly normal, 36% moderately disturbed, and 19% severely disturbed.

Findings

Measures of Outcome

32% of the total population were failures and 68% successes; percentages were comparable for schizophrenia and other diagnoses.

Table I shows that other diagnoses have a slightly superior but non-significant ($p>0·1$) distribution of social-adjustment scores. 26% of the total population showed a very satisfactory or full social adjustment (93% of these were rated nearly normal in behaviour), whereas 22·8% made a definitely poor adjustment; 18·9% were intermediate between these two social-adjustment categories.

TABLE I—SUCCESSES AND FAILURES

Diagnosis	No. of cases	Successes (%) by level of social adjustment			Failures (relapse in 1st year) (%)
		Full (3 points)	Partial (2 points)	Poor (1 and 0 points)	
Schizophrenia	156	25·2	17·4	25·8	31·6
Other	73	28·8	21·9	16·4	32·9
Total	229	26·3	18·9	22·8	32·0

Table II shows the distribution of the three-fold behavioural ratings by schizophrenia and other diagnoses and by success or failure. 40·8% of the total population were rated nearly normal, 35·2% moderately disturbed, and 24·2% severely disturbed. The ratings are related to success or failure.

Relation of Outcome to Clinical State on Discharge

The two indicators obtained from patients' case-notes ("discharged against advice", and "recovered", "relieved", or "not improved" on discharge) were both related to our criteria of outcome. (With the criterion of success or failure both showed a coefficient of con-

TABLE II—BEHAVIOUR

Diagnosis	No. of cases	Nearly normal (%)		Moderately disturbed (%)		Severely disturbed (%)	
		Success	Failure	Success	Failure	Success	Failure
Schizophrenia	156	37·8	1·3	23·1	11·5	7·7	18·6
Other	73	38·9	5·6	20·8	15·3	6·9	12·5
Total	229	38·2	2·6	22·4	12·8	7·5	16·7

tingency * of 0·24, p<0·001; with the three-fold social-adjustment rating the coefficients were 0·32 and 0·26 respectively, p<0·01.)

The rating of patients' level of behaviour was also correlated with outcome, both in terms of success or failure, where C was 0·50 for the schizophrenics and 0·38 for the others (p<0·001), and of social adjustment, which was rated in part on observations of patients' behaviour.

It is therefore clear that, in assessing subsequent relationships between clinical and social factors and the patients' outcome, a first precaution must be to ensure that the relationship is not a reflection of the patients' differing levels of clinical state at discharge. In many of the following instances the above indices of clinical state at discharge have been used to counteract crude clinical bias.

Pre-discharge Items

Number of previous admissions.—The relationship of this item to outcome differs for the two diagnostic categories, schizophrenia and other diagnoses. 31% of the schizophrenics were first admissions, and only a few (17%) had been in hospital three or more times before. This small category contained relatively more failures (12 successes and 15 failures, p<0·01) but showed no relationship with social-adjustment scores. In contrast, other diagnoses had a greater number of first admissions (44%), of whom only 3 of 32 failed. In this diagnostic group the number of failures increased significantly in the group of patients who had been in hospital before, compared with the first admissions (21 of 41 failed, p<0·001). Again no relationship was found with social-adjustment scores.

Length of key admission.—For neither schizophrenia nor other diagnoses did the length of key admission bear any direct relationship to success or failure; nor for other diagnoses did it relate to social-adjustment scores. However, for schizophrenia those with poor adjustment were mainly concentrated in those with less than ten years' stay (p<0·05); although trends are not striking, schizophrenics with longer stay in hospital had a slightly superior outcome.

Age at discharge.—Only 2 of the 17 schizophrenics aged more than 55 failed. Otherwise age bore no relationship to success or failure either for schizophrenia or for other diagnoses. As regards social adjustment, however, the younger schizophrenics, aged 20–34, were significantly more often poorly adjusted (p<0·01), whereas other diagnoses showed no such relationship.

Pre-admission levels of social achievement.—Various measures of pre-admission achievement were obtained in the areas of employment and economic responsibility. Superior achievement was usually significantly related to post-hospital success and to higher social-adjustment scores. The relationships still remained when clinical state at discharge was taken into account.

Post-discharge Experiences and Outcome

The two most important factors in the social experience of a discharged patient were whether the patient worked or not and with whom he lived.

Employment.—Table III shows an important relationship between employment and success or failure. 41% of the population worked for six months or more, and of these 97% succeeded, whereas of the 43% who were never employed only 46% succeeded. Of the 89 successful patients who worked for most of the year a third were rated as either moderately or severely disturbed, and many of the others had residual symptoms, indicating that the presence of psychotic symptoms was not necessarily a serious obstacle to their employment.

* Uncorrected coefficients of contingency derived from χ^2 results are used. The maximum for a 2 × 2 relationship is 0·707 and 3 × 3 is 0·816.

TABLE III—EMPLOYMENT

Employment	Successes	Failures	Total
6–12 months	89	3	92
1–6 months	19	18	37
Unemployed (includes those working less than a month)	44	52	96
Information inadequate for rating	4	..	4
Total	156	73	229

Type of living group.—The results so far presented take on new significance when tabulated by type of living group to which the patient returned. The significance of the social setting on discharge has been more fully analysed by one of us (G. W. Brown, unpublished); only the chief points are noted here.

Table IV shows that schizophrenics who returned either to parents, wives, or hostels relapsed in the first year significantly more often than did those returning to other kin (mainly siblings) and lodgings. Those who did succeed while living with their parents had significantly lower social-adjustment scores than patients living with other kin or in lodgings. Fewer living with parents were employed compared with the successful patients living with their wives, with other kin, or in lodgings.

Relatively more patients rated not improved on discharge went to stay with their parents or in hostels; but these differential failure rates and social-adjustment scores still persisted at a significant level when this bias was controlled. This indicates that the type of living group to which a patient goes after leaving hospital may have an important bearing on his subsequent career, whatever his residual disabilities are.

Psychiatrists are familiar with the mother who tolerates, and perhaps even encourages, an attitude of child-like dependence in her schizophrenic son. This kind of relationship was especially common in the 53% of unemployed schizophrenics living with their parents and was very rarely found in other types of living group. Perhaps it is not always beneficial for a schizophrenic to return to the close emotional ties of a parental or marital household.

There was some evidence that behaviour deteriorated more in schizophrenic patients who went to parental and marital groups. For example, the relative incidence of violent outbursts and displays of temper was significantly greater in these groups, whereas other psychotic manifestations (e.g., delusions) were more often reported for patients living with other kin and in lodgings.

Where a schizophrenic lived with his parents and was unemployed, with the result that he was brought into close contact with his mother all day, he was likely to fail; but if he or his mother were away at work for part of each day, he was more likely to succeed.

TABLE IV—WHERE LIVING

Where living	Schizophrenia			Other diagnoses		
	Successes	Failures	Total	Successes	Failures	Total
Hostel	6	7	13	4	7	11
Hostel (supportive)	1	..	1	4	3	7
Parental	55	31	86	8	8	16
Marital	7	7	14	16	1	17
Other kin (mainly siblings)	20	4	24	9	3	12
Lodgings	18	..	18	8	2	10
Total	107	49	156	49	24	73

TABLE V—MARITAL STATE

Marital state	Schizophrenia		Other diagnoses	
	Successes	Failures	Successes	Failures
Married	7	7	16	1
Widowed, separated, or divorced	16	2	11	14
Total	23	9	27	15

The relationship of outcome and post-hospital living group was less clearcut in the patients with other diagnoses, but there was some evidence that they, unlike the schizophrenics, tended to do better in situations involving close personal relationships. For example, table v shows completely contrary results for patients of the two diagnostic groups in respect of their marital state at discharge.

Of the 16 patients with other diagnoses who succeeded in a marital setting 7 were unemployed. In contrast, of the 7 schizophrenics who succeeded in a similar environment 6 were employed. These figures suggest that wives found it easier to tolerate a state of dependence in patients of the former group. A factor which may have contributed to this greater tolerance was the presence of a physical ætiology or physical handicap in 6 out of the 7 unemployed men in this group. These patients were easier to live with and responded more positively to the support offered to them than did the schizophrenic husbands, whose behaviour in several instances was much disturbed.

Aftercare

Only 37 of the 229 patients (16·2%) were reported to have attended an outpatient clinic for follow-up treatment. One or more visits were paid by a psychiatric social worker to 39 patients (17·0%). In neither of these small groups did the outcome differ significantly from that of the remainder.

Social Liabilities Incurred

To reach a just estimate of the outcome of these patients it was necessary to take into account not only their success in avoiding relapse and in attaining a fair level of social adjustment but also the consequences to other persons of the patients' return to living in the community. In some instances the patient's success was bought at the price of occasioning severe distress to others in his household.

A three-fold rating was therefore made of the amount of hardship which the patient's presence imposed on other members of his living group. The rating " severe liability " was reserved for those cases in which the patient's deranged behaviour caused considerable hardship to others—e.g., through violence (which was displayed by 63% of patients in this category), sexual deviation, callousness, paranoid accusations, and threats of suicide.

Where the patient's behaviour caused less serious hardship, the rating " moderate liability " was given; and patients whose symptoms, if noticeable at all, caused no obvious distress to others were rated " minimal liability ". This estimate was influenced by the attitude of the other members of the household, some of whom found even slight psychotic symptoms very disconcerting, whereas others (especially certain mothers) showed extreme indulgence.

17% of the total sample were rated severe liability, 28% moderate liability, and 55% minimal or no liability. Many of the patients who caused distress to others (79% of those rated severe and 44% of those rated moderate liability) relapsed within the year.

The category severe liability included 16 patients who were discharged against medical advice, either after an escape or at their relations' behest, but proved too difficult to cope with in the home, as in the following example:

Case 1.—Discharged after his third admission for schizophrenia, which he had had for eleven years. Still profoundly disturbed: liable to attack his mother and step-father in sudden outbursts. These attacks were tolerated, but when he began to make sexual demands on his sister he was returned to hospital.

Among the 156 successes there were 36 patients (23%) who caused moderate hardship to others and 8 whose presence in the household caused severe hardship. In the latter group it was evident that the burden of a very disturbed patient had only been transferred from the hospital to the home. 4 of these patients lived with their parents, 3 with their wives, and 1 with a foster-sister.

At the other extreme, patients rated as minimal liability tended to have a favourable outcome, except for 24 men who went to live in Rowton Houses, Salvation Army hostels, or other institutions. 11 of these returned to hospital, for the most part of their own choice. These probably form part of the group of long-stay patients referred to in the Royal Commission report as " having reached the stage at which they could return home if they had a reasonably good home to go to ".

It is in the intermediate category of patients presenting moderate liability that attitudes of persons in their immediate environment might especially be expected to influence the outcome. A typical example was the following:

Case 2.—Schizophrenic, aged 26, taken home against advice. Remained at home nearly two years although not well enough to work; often hallucinated, afraid to be left alone, and conspicuously strange in manner: " You could not take him out to meet people ". Parents lived in a genteel suburb and were embarrassed by son's appearance; their social activities were much restricted while he was at home.

Discussion

Previous follow-up studies have emphasised the diminishing chances of recovery of patients whose stay in mental hospital is prolonged; Smith (1946) and Stringham (1952) reported a poor outcome for the discharged chronic psychotic. In contrast, the present study showed that 2 of 3 long-stay patients succeeded in remaining in the community for at least a year after discharge; and that 2 of 3 of these successes were maintaining a viable social adjustment. In contrast to the usual findings with early cases, the outcome bore little relation to the patients' ages, recorded diagnoses, or length of stay in hospital; it did, however, bear a significant relationship to the social group to which they returned and to their employment record.

It is no new discovery that it is sometimes inadvisable for schizophrenic patients to return to their own families; the point has been made in many of the standard textbooks of psychiatry, and it provides one of the arguments in favour of foster-homes. The present study, however, makes it possible to support the assertion with a substantial series of instances. Freeman and Simmons (1958), discussing the outcome of male psychotics discharged after a short stay in hospital, contrast the outcome of those who returned to conjugal and to parental settings and conclude that wives have higher expectations of performance in relation to the recovered patient than do parents. Patients are just as likely to fail in the conjugal

setting, but if they survive they do so at a higher level of social functioning.

The importance of employment as a preventive of relapse is emphasised by Cohen (1955), who showed that, when chronic schizophrenics left a Veterans' Hospital, their success in avoiding relapse was not related to the continuance of minor symptoms but was significantly related to their success in finding work; and that this, in turn, was related to the amount of vocational planning before the patients left hospital. The present study suggests that employment is not only beneficial for the patient but also makes it easier for the household to tolerate a mentally handicapped member. In this connection it may be noted that many of the patients who were unemployed were judged by the investigators to be capable of working. If they could have been offered sheltered employment pending their return to normal work, their chances of survival in the community would have increased.

To help in finding jobs and suitable accommodation is a principal function of the psychiatric social worker. It is no adverse criticism of them but rather a reflection of the volume of work which they have to undertake, that so few of these patients were able to profit from their services. Nor were the patients the only ones who needed social-work help. The assessment of "distress caused to others" revealed that in many cases the patient's household needed help in dealing with problems presented by his return. "Community care" will not represent an advance in treatment if it means that a burden has merely been transferred from the hospital to the family. As was shown some years ago for shock treatment (Feldman et al. 1947), it may be necessary to intensify the provision for aftercare so as to derive the full benefit of the new emphasis on extra-hospital treatment of the mentally disabled.

Summary

A follow-up inquiry was completed with 229 of 240 patients discharged after more than two years' stay in a mental hospital.

68% of these patients succeeded in remaining out of hospital for at least a year, and 66% of these were rated as showing either full or partial social adjustment.

Successful outcome was associated with patients' clinical state on discharge, with their subsequent employment, and with the social group to which they went: patients staying with siblings or in lodgings did better than those staying with parents, with wives, or in large hostels.

In this group of patients the outcome bore little relation to patients' age, recorded diagnosis, or length of stay in hospital.

The social liability presented by these patients to their households was estimated.

The need for supportive social work with ex-patients and their families is pointed out.

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PSYCHIATRIC RESEARCH IN THE STATE OF ILLINOIS

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IN the past ten years an astonishing change has transformed the field of psychiatric research. At one time this field was almost equally barren of ideas, workers, and money. A few small groups kept up a brisk pioneering enterprise, but the massive support available to other fields of medical research was lacking. This has now quite changed, and the ideas, the workers, and the money are accumulating at an ever-increasing rate. The ideas are those fruitful hypotheses of the chemical basis of schizophrenia that are leading to so much biochemical, pharmacological, and physiological work on the ætiology of the psychoses.[1] The new biochemical insights gained and the new drug therapies such as the group of phenothiazines have revolutionised psychiatry, as Dr. Percival Bailey has recently proclaimed. But the present article will be concerned with another aspect of this progress—the very essential one of the financial and administrative machinery that has made all this possible. The increase in momentum of psychiatric research has been more noticeable in the United States than in England, and nowhere has this been so more than in the Department of Public Welfare, a branch of the State Government of the State of Illinois. Psychiatric research in the United States is supported from four main sources—the great private Foundations, the Federal Government, the Armed Services, and the individual State Governments. Each of these make contributions to the total, but this article will be concerned with just one part of one of these with which I am familiar.

In 1949 the Legislature of the State of Illinois decided that the only way to combat the ever-rising costs of care of the mentally ill was to organise research in psychiatry. A plan was devised whereby money paid to the State by the patients and the relatives of patients in the State psychiatric hospitals should be devoted to psychiatric research and training. This money contributes towards a special Mental Health Fund which is devoted to six main projects: (1) psychiatric research, (2) training of medical, nursing, and other professional staff, (3) mental health education of the general public, (4) community mental health services, (5) service improvement projects (i.e., studies of the system designed to improve its efficiency), and (6) administrative costs of the other five projects (e.g., the cost of collecting the money from relatives).

The fund runs on a biennial budget, and this for the years 1957–58 amounted to $24,000,000, of which some $7,000,000 came from the payment made by the patients and their families. The portion of this devoted to psychiatric research and training during this two-year period was some $4,000,000, of which about half was devoted to research. This fund is administered by a special body—The Psychiatric Training and Research Authority set up within the Department of Public Welfare with the advice of the Illinois Psychiatric Advisory Council to which members are appointed by the Governor and which meets once a month. It consists of the heads of the Department of Psychiatry of the Chicago medical schools, of the Michael Reese Hospital (a leading centre for psychosomatic

1. Smythies, J. R. *Lancet*, Aug. 9, 1958, p. 308.

medicine), and of the Institute for Psychoanalysis as well as Dr. Otto L. Bettag, the director of the Department of Public Welfare.

The main centre of psychiatric research in Illinois is not set in Chicago as one might have expected but in Galesburg, a pleasant little town of some 30,000 inhabitants in Western Illinois. The Galesburg State Research Hospital is one of the only five hospitals in North America that has been fully accredited by the American Psychiatric Association and is one of the most modern and up-to-date hospitals in existence. It is built on the villa principle, and each villa holds 30–40 patients. The research laboratory is directed by Dr. Harold E. Himwich, a ranking authority on the chemistry of the brain, and the work is devoted to studies of the biochemistry and pharmacology of the nervous system. Important work has been done on the pharmacology of the reticular formation and of hallucinogenic and phenotropic drugs, on the biochemistry of maturation and ageing, on the chemistry of psychosis, the clinical evaluation of new drugs, and other related subjects.

But I am dealing with administration rather than with the research itself, and it will interest British readers to learn that the research budget of the laboratory for funds devoted solely to salaries, equipment, and materials is $883,220 for the biennium, the significance of which I will return to below. The State also supports at Elgin State Hospital a biochemical laboratory that operates on a budget of $148,000 with other sources of funds outside the State and two projects at Manteno State Hospital under Dr. Nathaniel Aptner at a rate of $66,000 a year. The Mental Health Fund also finances a large number of projects in the universities of the State. The main one of these is the Illinois Neuropsychiatric Institute (a section of the University of Illinois). Here work is being carried out in neuropathology, on the tissue-culture of neurones, and on biochemical changes in schizophrenia. Twelve other projects are being conducted in various branches of the University of Illinois bringing its yearly share to $350,000. The University of Chicago has two projects at $80,000; the Michael Reese one at $34,000; Chicago Medical School one at $23,000; and Loyola University one at $26,000. These projects cover child psychiatry fairly substantially as well as purely biological problems.

In spite of this lavish outlay, income for the first few years of the projects has accumulated faster than it was spent, and these accumulated funds have been used to build two new psychiatric research hospitals in Chicago. The Illinois State Psychiatric Institute is now complete at a cost of $9,000,000 and is truly a magnificent building. It will be run by the Department of Public Welfare and staffed mainly by five services from the Chicago medical schools. The second hospital will cost $5,500,000 and is a pædiatric hospital for mental defectives. These two hospitals will undertake extensive research and training of psychiatrists.

Now to devote some attention to the input side of the money flow—to use a cybernetic analogy. The charges for inpatient care in the State hospitals are set by the Department of Public Welfare for each case after a careful consideration of the patient's financial resources and these charges vary from a maximum of $81 a month to nothing. The patient or his family is free at any time to dispute these charges in the courts, although this is in fact very seldom done. It should be remembered that there is no National Health Service of any kind in the United States, and so people expect to pay for the services that they receive in hospitals.

In conclusion it is interesting to note that the research budget of the Galesburg State Research Hospital (spent wholly on salaries for research workers, goods, and equipment) is $441,600 a year. The total expenditure from Government sources in the U.K. for the year 1957 on psychiatric research came to £83,000[2] which is equivalent to $410,000 (counting £1=$5, the cost-of-living equivalent).

The enlightened mental health research programme of the State of Illinois is financed by those personally most interested in the discovery of the cause and cure of mental illness—the patients themselves and their families—whereas the total cost of maintaining the patients is borne by the State. This bold scheme is already spreading in the States and has been adopted by Louisiana. As it is a much smaller and poorer State than Illinois its research and training budget is only $350,000—which is nevertheless a respectable sum.

I am most grateful to Dr. Otto L. Bettag, director of the Department of Public Welfare, and to Dr. Lester H. Rudy, superintendent of the Galesburg State Research Hospital, for making available the facilities that have made this report possible.

Medicine and the Law

Tale of Two Patients

A CORONER'S jury has returned a verdict of death by misadventure in a case in which the wrong patient was discharged from hospital.[3]

A Mr. Grange, who had been involved in a road accident, and who apparently had some deformity, was admitted to hospital at about 11 P.M. after being knocked down by a motor-car. He was found by the casualty officer to be "moderately shocked" and was put to bed under observation. An elderly man, also a road-accident case, was admitted the same evening; after treatment, his discharge was arranged provided that his own doctor was known so that a letter could be sent to him.

The casualty officer went to bed, and was awakened at about 2 A.M. by his staff nurse. She and another staff nurse apparently inquired if the crippled man could go home. When the casualty officer did not answer, one of them added: "the person under observation". The casualty officer then said that the man could go if he had a letter for his doctor.

The casualty officer was awakened again at 6 A.M. and was told that a doctor had telephoned to say that he was returning a patient because he thought he was suffering from internal hæmorrhage. It was then that the casualty officer discovered that Mr. Grange and not the elderly man had been allowed to leave. Mr. Grange died a few hours later.

At the inquest a consultant surgeon said that, ideally, the patient's record card should have been taken to the doctor. "That is being wise after the event."

The coroner told the jury: "It might seem to you that things have been rather lackadaisical . . . but there is no evidence of negligence of a kind which is likely to lead to a charge of manslaughter." It would be wrong for them to word their verdict in a way that might show that they were trying to decide some question that could be settled in a civil court.

The coroner also told the jury that he did not think it necessary for them to add anything to their verdict, as senior officials of the hospital were present. "I feel that we can rely on the hospital, if there is need for tightening up to be done."

2. *Hansard*, Jan. 27, 1958, col. 24. This figure is taken from a written report by the Minister of Health. It includes £58,000 from Exchequer funds spent by the Medical Research Council and £25,000 spent within the National Health Service. It does not include expenditure on research in universities and medical schools.
3. *Newcastle Journal*, Sept. 12, 1958.

Public Health

BRONCHITIS AND THE ACIDITY OF URBAN PRECIPITATION

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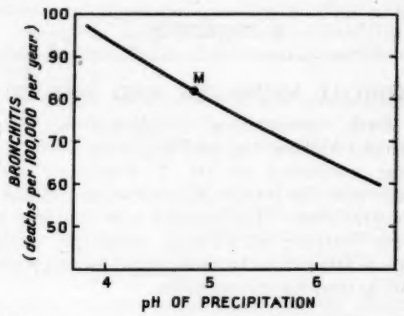
THE incidence of bronchitis is uncommonly high in Britain, especially in urban areas during winter; and it has been conjectured that air pollution is at least partly responsible. In this paper I report a correlation between bronchitis mortality and the acidity of urban precipitation.

The mortality-rates for bronchitis were calculated from the Registrar General's annual statistical reviews for the whole populations of fifty-three county and Metropolitan boroughs in England, Scotland, and Wales over the five-year period 1950–54, and plotted on scatter diagrams versus air-pollution data from single stations and periods within these boroughs. These latter data were extracted from table 8 of the 27th report of the Department of Scientific and Industrial Research on the investigation of atmospheric pollution (1955), which provides figures for the monthly atmospheric deposit of tar, ash, other combustible matter and sulphate per unit area in urban districts, and also gives the pH of the precipitation. Of all these, only the last two showed any obvious relationship with the bronchitis death-rates, and a more detailed statistical treatment was then carried out, using in this case averages of all the pH and sulphate values given for the winter months September to March in each of the fifty-three boroughs. To obtain a more normal frequency distribution, and also a more linear regression, a logarithmic transformation of the bronchitis death-rates and of the sulphate deposits was employed.

The logarithmic correlation coefficient (r) for bronchitis and winter pH of precipitation amounted to $-0{\cdot}49$, a value significant at the 1% level. The corresponding coefficient for bronchitis mortality and winter sulphate deposit, which is no doubt related to the production of sulphur dioxide from fuel combustion, amounts to $+0{\cdot}32$, a value significant only at the 5% level.

To test further the above relationships, partial correlations of bronchitis mortality with the pH of winter precipitation and with the winter sulphate deposit were carried out, in order to eliminate the effects of any correlation between the two environmental variables. Following this procedure, the coefficient of correlation (first-order) between bronchitis mortality and pH of winter precipitation fell only slightly to $-0{\cdot}45$, a value still significant at the 1% level. In contrast, the correlation with sulphate deposit declined considerably, the first-order coefficient of $+0{\cdot}24$ being no longer significant even at the 5% level. It is therefore unnecessary to consider this last correlation further.

The partial regression equation relating bronchitis mortality (b, as deaths per 100,000 of population per year) to the acidity of winter precipitation (a, as pH) is $b = 192\ (0{\cdot}838)^a$. This relation is shown graphically in the chart, from which it may also be seen that the logarithmic average of the annual urban death-rate from bronchitis is 82 per 100,000 persons, or about 1·8 times the rural death-rate for the same period. In those areas where rain pH is below 4, and hence strongly acid, the death-rate reaches 100, while it is only about 60 in those urban areas with the least acid rainfall. The rural death-rate for the same period is considerably lower even than this, at 46 annually per 100,000 of population; so acidity would not appear to be the only factor involved in the increased



The relation between bronchitis mortality and acidity of precipitation in urban areas. M gives the logarithmic mean death-rate.

urban death rate, if in fact the acidity correlation is taken as truly causal. While such an interpretation must of course be regarded with caution, it seems not unreasonable to infer that long-continued exposure to acid aerosols might increase the likelihood of bronchial inflammation. In this connection it must be borne in mind that during dry weather the aerosol droplets will be considerably more acid than the ultimate raindrops in which they are precipitated, and may well exhibit pH values below 2 at times.

Even in predominantly rural areas the rainfall may be quite strongly acid. For instance, in the English Lake District rain pH averages less than 4·5, and goes below 4 on occasions, owing to atmospheric supply of sulphuric acid with easterly winds from the great industrial areas (Gorham 1958a). Surprisingly, however, in the industrial cities themselves hydrochloric acid seems likely to be the chief cause of low pH values (Gorham 1958b). The effects of both these strong mineral acids on bronchial tissues might well repay detailed investigation.

I am much indebted to Mr. David Driver for help with the calculations.

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Strontium 90 and Malignant Disease

A report in the *New York Times* of Sept. 20 refers to new work on the important question of whether or not there is a threshold level of ^{90}Sr in bone, below which no bone cancer or leukæmia is induced. The work is that of M. P. Finkel at the Argonne National Laboratory in Lemont, Illinois, and it is described in detail in *Science*, in an issue which has not yet reached us. ^{90}Sr was injected in varying doses into 810 mice, and the incidence of tumours and length of life in this group was compared with those of an uninjected control series. According to the *New York Times*, the results suggested that no damage was done by small doses—in other words, there *was* a threshold in mice. From observations in cats and dogs, however, Miss Finkel estimates that ^{90}Sr is probably " seven to fourteen times more harmful to man than to mice, because of his greater size and other factors ". Her conclusion is that the threshold for man is so much higher than present fallout levels that fallout is extremely unlikely to induce " even one bone tumor or one case of leukemia ".

On the assumptions that no threshold exists and that weapon tests stop this year, the recent United Nations report [1] estimated that fallout radiation may produce 400 to 2000 cases of leukæmia a year. Assuming a threshold of 400 rem, the U.N. Committee's figure for fallout leukæmia dropped to zero.

1. See *Lancet*, Aug. 16, 1958, pp. 355, 360

Congresses

TROPICAL MEDICINE AND MALARIA

THE Sixth International Congress of Tropical Medicine and Malaria was held in Lisbon on Sept. 5–13 under the presidency of Dr. J. FRAGA DE AZEVEDO (Portugal), with Sir PHILIP MANSON-BAHR (U.K.) as an honorary president. The palatial new building of the Portuguese Institute of Tropical Medicine, which has had fifty-six years of vicissitudes since its inception, was ready just in time for this occasion.

Acclimatisation to Heat

SID ROBINSON (U.S.A.) summarised physiological adaptations to heat as (*a*) improvement in efficiency of evaporative cooling and in sensitivity and capacity of the sweating mechanism; (*b*) increase of circulating blood-volume during exposure, accompanied by improvement in circulatory stability; and (*c*) dramatic improvement in temperature regulation so that by the 8th day of exposure, men may perform work in heat with no greater elevation of rectal temperature or metabolism than when they perform the same work in a cool environment.

D. E. BASS (U.S.A.), however, reported a recent finding of venoconstriction and reduction of blood-flow in the forearm during work in heat, occurring only on the 3rd and 4th days of exposure, and suggested that such venoconstriction might improve cardiovascular performance by maintaining functional blood-volume; this led him to reconsider the concept that cardiovascular improvement resulted from actual increase in basal blood-volume.

W. V. MACFARLANE (Australia) discussed human water economy in the heat, aldosterone, and several interesting seasonal differences in body responses to fluid loss. In winter, for example, plasma-volume did not fall on the loss of 3 litres of sweat, nor did antidiurectic substance (A.D.S.) appear in the plasma; in summer, plasma concentrated with the same sweat loss and A.D.S. appeared.

C. S. LEITHEAD (U.K.) reported a significant fall in hæmatocrit and circulating protein levels in men on their 4th day of exposure to heat in Kuwait, and interpreted this as evidence of increase in circulating blood-volume by hæmodilution. Prior to this, tilt-board and exercise tests had revealed cardiovascular instability of the subjects, but giddiness and syncope appeared only in those who had never before been in the tropics and to whom, therefore, all was strange—climate, environment, and customs.

This possibly cerebral effect was emphasised by E. M. GLASER (U.K.), who observed that acclimatisation to heat depended partly on stored information which modified some heat-regulating responses and which resembled habituation and learning. Subjective responses to warming were also modified during acclimatisation to heat, and it seemed possible that this was also due to a cerebral mechanism of habituation.

Heat Tolerance

R. K. MACPHERSON (U.K.) described "heat tolerance" as a simple title for a complex subject. When a man exposed to heat collapsed, the limit of physical tolerance had obviously been reached and passed; but long before that stage the man's powers of perception, reason, and judgment were impaired and it was difficult to say when such deterioration began. Tolerance was also to some extent *affective* in that there would always be a limit to the willing endurance of discomfort.

H. S. BELDING (U.S.A.) mentioned at least eleven indices or scales of heat stress, including the heat stress index (H.S.I.) recently proposed by Professor Hatch and himself.[1] Before accounting for such variables as sex, age, and degree of acclimatisation, it was first necessary to achieve an index valid in application to young, fit, and fully acclimatised men. Even then, the factors affecting heat stress were formidable enough: temperature of air, solid surroundings and skin, ambient skin and vapour pressures, air speed, body-surface area and postural attitude, body-heat production, clothing, and time of exposure. Each factor required quantitative assessment, and deficiencies of the present H.S.I. lay in misestimates of the circulatory strain imposed upon the subject, his skin temperature, and the effects of clothing.

The problem of whether men working in spaces where radiant-heat load is severe (e.g., at furnace doors) be clothed or seminude should be one of concern to industrial medical officers. Professor Belding believed that clothing importantly reduced heat stress by blocking radiation and convection. He conceded that it might reduce evaporation from the skin but argued that increased sweat production which wetted the clothing and thus gave a larger total surface for evaporation would be compensatory.

F. N. CRAIG (U.S.A.) from a study of the physiological state of subjects at the end of their tolerance-times (i.e., the time period elapsing before voluntary withdrawal from environmental heat stress) concluded that the total heat stored in the body was the critical factor in tolerance of heat stress. As heat storage was calculable from metabolic rate, thermal resistance of clothing, and environmental temperature and humidity, he suggested that this was a method of predicting heat tolerance.

F. H. BONJER (Netherlands) described experiments on men working at a brick furnace. In such situations, managers wished to know the maximum allowable working-time and the minimum required rest period after exposure. As the minimum heat gain of the body was calculable for a given set of circumstances, the maximum allowable working time could be computed by dividing the presupposed maximum allowable heat gain (i.e., 1°C rise in body-temperature, or 60 KCal in a man of average size) by the minimum heat gain per unit of time. Derivation of minimum required rest period after exposure was more complex and required further investigation.

A. R. LIND (U.K.) said that in emergencies such as rescue operations in coalmines, men were sometimes required to work in environments too severe to fall within the range of existing indices of heat stress. He had found, however, that a simple weighting of wet (×0·85) and dry (×0·15) bulb temperatures related climates of similar severity, and this formula proved effective for wide variations of energy expenditure and clothing worn, although the range of air-movement investigated was limited.

D. M. KERSLAKE (U.K.) said that heat-stress effects due to small increases in absolute humidity were large when the skin was completely wet with sweat, and recent experiments showed that they were much smaller when evaporation of sweat was complete. Effects on skin and mouth temperatures and on sweat-rate of resting subjects exposed to the same dry-bulb temperature (36°C) and air movement but to a wide range of absolute humidity accorded with expectation, and transition from partial to complete wetness of skin appeared to be abrupt and occurred at the expected level of absolute humidity (37 mm. Hg).

Heat Illness

W. P. STAMM (U.K.) discussed the nomenclature and classification of heat illness. The present W.H.O. International Statistical Classification contained terms and concepts now archaic, and modifications proposed recently to the Climatic Physiology Committee of the Medical Research Council [2] were handicapped by an attempt to remain within existing W.H.O. framework and coding.

1. Belding, H. S., Hatch, T. F. *Heating, Piping, and Air Conditioning*, 1955, **27**, 8, 111.
2. Weiner, J. S., Horne, G. O. *Brit med. J.* 1958, i, 1533.

F. P. ELLIS (U.K.) read a paper by W. S. S. LADELL (U.K.) on anhidrotic heat exhaustion. This appeared to be fundamentally an endocrine disorder, as inability to retain salt and water accompanied anhidrosis, but failure of target organ responses was more likely than a central "stage of exhaustion" because treatment with posterior pituitary extract or deoxycortone acetate did not always help. J. P. O'BRIEN (Australia), unable to attend, sent his belief that the disorder was purely local in origin. That facial hyperhidrosis was found in the presence of anhidrosis elsewhere, and that the anhidrotic areas began to sweat if treated with anhydrous lanolin, were points which seemed to discount a hormonal basis.

J. GUTHRIE (Kuwait) reported that heat illness, usually heat hyperpyrexia and salt and water depletion syndromes, had a much higher incidence among oil-tanker crews in the Persian Gulf than among those living and working ashore in Kuwait. This was due to lack of adequate air-cooling on shipboard, and to unsuitable habits of the sailors exposed. Some 20,000 pamphlets, in eight languages, offering simple instructions in prevention of heat illness had been issued to ships calling at Kuwait; this appeared to have had good effect, as marine cases diagnosed there in the past three years numbered 222, 137, and 63.

G. P. CROWDEN (U.K.) wished for a wider use of simple measures to ensure health in the tropics. Whitewashing the exterior of a corrugated-iron structure reduced the temperature within. When cotton mosquito nets, the meshes of which were often occluded by fibrils, were applied to a hospital bed, air velocity over a possibly febrile patient was reduced to an eighth of its former level, but synthetic fibre mosquito netting did not have such a major disadvantage. Bright metallic surfaces such as were afforded by aluminium foil had a high reflectivity and low emissivity for radiant heat, and were therefore of value in heated industrial spaces.

M. TOOR (Israel) described experiments on two groups of fully acclimatised men in the Dead Sea area.[3]

D. MINARD (U.S.A.) discussed prevention of heat casualties among Marine Corps recruits training at Parris Island, South Carolina. Changes in hot-weather training regulations for 1956 included adoption of a heat-stress index based on weighted readings of dry-bulb, wet-bulb, and globe-thermometer readings (wet-bulb/globe-temperature index of Yaglou [4]). This index was chosen because of the simplicity of the instruments involved. Use of the index to modify or restrict training of recruits at certain levels of heat stress reduced heat casualties from 12·4 per 10,000 in 1955 to 4·67 per 10,000 in 1956.

Nutrition

One of the major problems of tropical countries is malnutrition in the young.

O. BASSIR (Nigeria) reported that the addition of soybean flour to the maternal diet had a beneficial effect on the composition and volume of breast-milk.

O. A. ROELS (Belgian Congo) had noted that in African mothers on a staple diet the protein content of breast-milk fell during the first three months of lactation, that there was correlation between the vitamin-A, carotene, and fat content, and that there was no relation between content and volume of breast milk.

The changes in the blood picture in kwashiorkor in the first four weeks under treatment were described by F. WALT (South Africa). Over 60% of children with megaloblastosis of the bone-marrow were found to have kwashiorkor, and all the cases responded within ninety-six hours after injection of folic acid. Sudden severe falls in hæmoglobin level had been observed in cases of kwashiorkor with sudden acute infection, despite a constantly rising serum-protein level.

3. See *Lancet*, Sept 13, 1958, p. 579.
4. Yaglou, C. P. Annual report no. 9 to Commission on Enrivonmental Hygiene, U.S. Armed Forces Epidemiological Board.

G. FUHRMANN (Germany) described how his modification of the "arm-girth, depth-of-chest, and width-of-hip" index went some way to solve the difficulty of accurately assessing the state of nutrition.

K. HILL (U.K.) stated that infection or malnutrition or both are usually necessary for the development of veno-occlusive disease of the liver in response to ingestion of pyrrolizidine alkaloids.

G. MORETTI (France) had studied the enlargement of the parotid gland in cases of alcoholic cirrhosis in France and of malnutrition in Guinea. The histological picture in the two types was similar except that in the African cases interstitial fibrosis was a notable feature.

H. A. P. C. OOMEN (Netherlands) reported his studies in Indonesia on the response of the eye to malnutrition. Besides xerophthalmia, retrobulbar neuritis was very common, and though vitamin A was very important the part played by protein and fat in the well-being of the eye must not be forgotten.

An interesting condition of calcification of the pancreas in persons aged 15–30 in Indonesia was described by P. J. ZUIDÉMA (Netherlands). The patients required large amounts of insulin, had no steatorrhœa and no ketosis, but frequently had cataract. Such cases seemed to be the result of malnutrition, the calcification of the pancreas having been preceded by fibrosis.

Experimental aspects of tropical malnutrition was discussed by B. S. PLATT (U.K.), who described his observations in pigs, in which a low-protein, low-carbohydrate diet produced a greatly different response to a low-protein intake high-carbohydrate diet.

Trypanosomiasis

R. B. HEISCH (Kenya) announced the successful isolation of *Trypanosoma rhodesiense* from the bush buck and its transmission to two human volunteers.

Hæmoglobinopathies

C. TRINCÃO (Portugal) described the methods of identifying abnormal hæmoglobins. The principal technique was that of electrophoresis, but there were many others—chromatography, determination of solubility, resistance to denaturation by alkali or by cold, oxygen saturation, aminoacid composition, number of NH_2 and SH endgroups, and antigenic properties. Electrophoresis could be carried out at varying pH, by the open boundary technique, by zone electrophoresis on starch paste, starch gel, and agar, and by using various filter-papers or cellulose acetate as the supporting medium.

H. LEHMANN (U.K.) described the principal disorders. The most severe were the homozygous conditions thalassæmia major and sickle-cell anæmia; milder were the heterozygous thalassæmia minor and the homozygous states for hæmoglobins C, D, and E. Intermediary were mixed syndromes in which one gene for sickling and one for thalassæmia were inherited together or either of the two with that for another abnormal hæmoglobin. Additional stress such as pregnancy or infection could acerbate the less severe conditions so that the clinical condition resembled that of thalassæmia major or sickle-cell anæmia. In the world distribution of these abnormalities sickle-cell hæmoglobin overlapped the distribution of thalassæmia and hæmoglobin C; and thalassæmia was also common in Asia, where it contributed to the high incidence in some regions of hæmoglobin-E/thalassæmia and in a not yet fully understood way to hæmoglobin-H disease.

N. C. FERREIRA (Portugal) said that the fœtal hæmoglobin in thalassæmia was indistinguishable from that in normal infants.

R. J. CABANNES (Algiers) had found high incidences of hæmoglobin C in the High Volta, French West Africa. In certain regions there, 17·2% of the people were hæmoglobin-C trait carriers (AC) and 1·3% were homozygotes (hæmoglobin-C

disease). The heterozygotes were completely normal, and the homozygotes were comparatively little affected, though there was some anæmia and occasional pains in the joints and the abdomen with gastrointestinal upsets. There was some lability of the nervous system, which could be demonstrated in the encephalogram. Hæmoglobin K was commoner in North Africa amongst the Kabyles and was found only occasionally in West Africa.

LIE INJO LUAN ENG (Indonesia), in a paper read on her behalf, said that both thalassæmia and hæmoglobin-E/thalassæmia were seen regularly in Indonesia. These two were similar in their pleomorphism. Whether splenectomy had any therapeutic value was as yet not decided. Hæmoglobin-E disease was a mild hæmoglobinopathy, and the hæmoglobin-E trait caused no symptoms. In some people the hæmoglobin-E trait was associated with microcythæmia and with an increased resistance of the red cells to osmotic lysis.

A. R. NOGUEIRA (Portugal) reported on the abnormal hæmoglobins of Portuguese East and West Africa. In the East only sickling was found, but he could not confirm reports of some British workers who had described a very high incidence of sickling from Mozambique. In the West, Angola showed sickling only; but in Portuguese Guinea 14 instances of hæmoglobin N and 11 of hæmoglobin K had been found among 9224 samples. Some 20 samples containing a G-like hæmoglobin were still awaiting final identification.

F. B. LIVINGSTONE, W. ZUELZER, A. R. ROBINSON, and J. V. NEEL (U.S.A.) reported that some rare hæmoglobins—notably hæmoglobin N—were more frequent in Liberia than elsewhere. In some regions of Liberia they had also found patients with classical thalassæmia and also a thalassæmia or thalassæmia-like condition where adults possessed high proportions of hæmoglobin F without their red cells showing the morphological features of thalassæmia.

A. WOODRUFF (U.K.) reported on the results of work where blood had been taken from patients with sickle-cell anæmia, "labelled" with radioactive chromium, and reinjected. Following the fate of the radioactive cells it was found that there were two groups; one, amounting to about a third, was very short lived and disappeared in about four days, whereas the life-span of the remainder was only moderately reduced. By scanning the body surface with a scintillation counter it was possible to show that most of the cell destruction took place in the liver.

J. P. JONXIS (Holland) gave an account of the techniques employed in his laboratory for the recognition of the abnormal hæmoglobins. In sheep there were differences between the oxygen-saturation curves of two adult variants. So far no such differences had been noted in man. Even fœtal hæmoglobin did not differ from adult hæmoglobin in that respect—provided that it had been freed from stroma and been thoroughly purified by dialysis. Some hæmoglobinopathy-like conditions in which it had not been possible to find an abnormal hæmoglobin by current methods might turn out to be associated with abnormal oxygen affinity of the hæmoglobin.

A. I. CHERNOFF (U.S.A.) in a large survey, had found in North Carolina not only hæmoglobins S and C, but an appreciable number of samples with various "fast"-moving hæmoglobins. Hæmoglobin D was present in 1% of American Negroes.

L. W. DIGGS (U.S.A.) presented very full evidence that sickle-cell disease was a veno-occlusive disorder, the lesions occurring where blood was least oxygenated. He demonstrated the development from infarct by sickled cells to necrotic lesion and to repair by organisation in virtually all organs and all parts of the body. The spleen was most consistently affected. Other characteristic injuries were aseptic necrosis of the head of the femur and occlusive lesions in the periphery of the eyeground. The sickle-cell-trait carrier was not immune; he could suffer from splenic infarct when flying at high altitude in non-pressurised aircraft, and there was a specific hæmaturia.

J. C. WHITE and G. H. BEAVEN (U.K.) had compared the current methods of estimating fœtal hæmoglobin. Equally good results were obtained with them all, provided the concentration was above 5–10%. They improved the sensitivity of fœtal-hæmoglobin estimation by combining the alkali denaturation of the non-F hæmoglobin with the measurement of hæmoglobin F in the residue. Hæmoglobin F amounted to $80 \pm 10\%$ at birth, and was less than 10% at four to six months. Traces could be found up to five years. Values up to 20% were found in sickle-cell anæmia and up to 90% in thalassæmia major. Half of the cases of thalassæmia minor or of sickle-cell trait showed traces of fœtal hæmoglobin.

J. H. WALTERS and H. LEHMANN (U.K.) had examined liver function in sickle-cell anæmia. There was progressive deterioration with increasing age. This was reflected in a rise of the serum thymol-turbidity units and in a fall of the pseudocholinesterase level. Liver-biopsy specimens showed sinusoids filled with a network of silver-staining organic material which tended to form layers on the walls of the sinusoids.

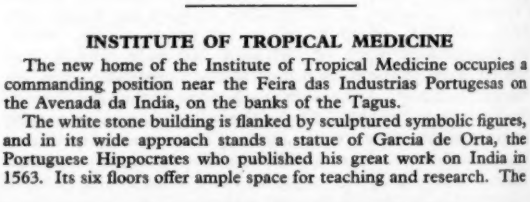
At a round-table discussion a resolution was prepared for the final plenary session of the congress:

"It is recognised that the hæmoglobin diseases present a major health problem in the countries where they are found—most of them tropical. Millions of people are affected in Europe, Asia, Africa, and the Americas. With the expected decrease of infectious diseases the importance of genetical disorders—amongst which the hæmoglobinopathies are foremost—will become greater rather than lessen. The encouragement is desirable of surveys of the distribution of thalassæmia and of the abnormal hæmoglobins. Though much has been done, there are still wide gaps in our knowledge. Without such information planning of public-health measures will be handicapped. With the rapid rate of discoveries of new hæmoglobins and new disorders a real risk arises that the nomenclature of these hæmoglobins and the terminology of these disorders become confused. This gathering of workers interested in the hæmoglobinopathies hopes that sooner rather than later steps will be taken to arrive at international agreement. As regards the terminology of clinical disorders cognisance is taken of the 'Recommendations' prepared by the Colonial Medical Research Committee Working Party on Sickle-Cell Trait and Sickle-Cell Anæmia, London published in *The Lancet* and *British Medical Journal* on May 25, 1957."

INSTITUTE OF TROPICAL MEDICINE

The new home of the Institute of Tropical Medicine occupies a commanding position near the Feira das Industrias Portugesas on the Avenada da India, on the banks of the Tagus.

The white stone building is flanked by sculptured symbolic figures, and in its wide approach stands a statue of Garcia de Orta, the Portuguese Hippocrates who published his great work on India in 1563. Its six floors offer ample space for teaching and research. The



two large air-conditioned amphitheatres, which can each seat 126 students, are equipped with head-phones and projection apparatus of all kinds. The three laboratories each provide working space for 60 students and independent tables for each. The institute has the following departments: hygiene and climatology, entomology and helminthology, dermatology and mycology, and bacteriology and virology. There is a special service for radioisotopes.

A special number of the annals of the institute has been published to mark the occasion. It gives a full history of tropical medicine in Portugal. It describes the schools of Goa, India; Loanda, Angola; Lourenço Marques, Mozambique. It shows the range of work of the institute's activities, which extend from Timor in the Indonesian Archipelago to the Cape Verde Islands.

In England Now

A Running Commentary by Peripatetic Correspondents

SOCRATES ON MEDICAL EDUCATION *

Alcibiades: Tell me, Socrates, how can we be sure that our doctors are well trained?

Socrates: Do you think it right, Alcibiades, that we should say of a pudding that it is good or bad?

Alcibiades: Certainly, Socrates.

Socrates: It must be possible then to distinguish a good pudding from a bad one?

Alcibiades: Of course it is, Socrates.

Socrates: And I suppose you would say that a good pudding must have good ingredients?

Alcibiades: That is so, Socrates.

Socrates: Tell me, Alcibiades, which ingredient do you think the most important?

Alcibiades: I think the flour is, for without the flour there could be no pudding.

Socrates: And whom do you consider the best judge of flour?

Alcibiades: I suppose the farmer, who grows the wheat, can best tell which is the best flour.

Socrates: And would you say the miller also has this knowledge?

Alcibiades: Yes, the miller also.

Socrates: So it would follow, would it not, that the farmer and the miller are amongst the best judges of what is a good pudding?

Alcibiades: It would seem so, Socrates.

In like manner Socrates persuaded Glauco to say that the poultry-keeper must judge the eggs, and Agathon that the vine-yard owner knew most about the raisins.

Then Apollodorus broke in: But Socrates, you have forgotten the honey!

Socrates: I was coming to the honey, Apollodorus, but tell me why you think it important.

Apollodorus: It gives sweetening and flavour to the whole pudding, Socrates. Why, half the pudding is the honey.

Socrates: That would surely mean putting a great deal of honey into a pudding!

Apollodorus: I do not mean half by weight, but through its pervasiveness honey is the other half of the pudding.

Socrates: How then would you judge the honey, Apollodorus? Would an Athenian who keeps bees be a suitable judge?

Apollodorus: No indeed, Socrates, for he does others things besides keep bees. The judge of honey must be a member of the bee-keepers guild from Hymettus.

Socrates: Well, when you have judged the ingredients there is still the mixing in the right proportions and the cooking at the right temperature. Would you include a cook amongst your judges?

Eryximachus: Yes, Socrates, we must include a cook, but we must be careful not to choose the one who cooked the pudding. It is well known that if a prize of 100 drachmæ were to be awarded for the best pudding no cook would think his own pudding worthy of less than 90 drachmæ.

Socrates: Where, then, would you find a cook to judge your pudding?

Eryximachus: If it is an Athenian pudding, to be on the safe side you must choose a cook from Sparta.

Socrates: But what will happen if the Spartans do not like the same kind of pudding as the Athenians? And do you think, Alcibiades, that all your judges will agree about the pudding? Or will the farmer, perhaps, say that his good flour has been spoiled in the mixing, and the raisin-grower that there is too much honey?

Then, turning to a boy who was sitting at his feet, Socrates said: Boy, you have heard what Alcibiades and the others have said. How would you decide whether a pudding is good or bad?

Boy: I would eat it, Socrates!

* The first meeting of the Association for the Study of Medical Education is being held in London this week.

For a congress on tropical medicine there could hardly be a more appropriate venue than Lisbon, with its long history of adventure and exploration. The hospitable Portuguese had rushed ahead with their new institute of tropical medicine, so that we could meet within its walls, though some of the rooms had not been finished. Indeed when we first arrived workmen were surging around with buckets of cement. The film room, which hardly existed on Sept. 4, was complete and in working order on the morning of Sept. 5. The main staircase had only been put in place four days before, and a gang of a thousand navvies worked all night to get the building ready for the congress.

Behind the information desks sat Portuguese ladies who, though sometimes a bit puzzled, were always most helpful, and we soon came to learn why these people are acknowledged as the kindest and most considerate in the world. Typical of their friendly and charming hospitality were the attractive stamps issued to commemorate the Congress, which showed gaily coloured birds, flowers, insects, and mammals from the Portuguese tropical possessions. At our meetings, social and scientific alike, everyone was pleased to meet everyone else, had something to impart, or questions to ask. It may well be that we all had diverse blood-groups or harboured different brands of hæmoglobin, but the antigen of good will was common to all.

* * *

A student of art learns to look for the characteristic touches of the master. He knows that certain themes recur frequently—perhaps the pattern of light thrown by a candle, or the gables of a house viewed from a characteristic angle. The same is true in science, and when this year I began to review half a century of progress in cardiac physiology I found that I recognised not only the style and mannerisms of some authors over the years, but sometimes also their hopes, their disappointments, and their regrets. There is a poignancy in the way they return to an idea or concept, born of some ancient intellectual anguish but fated by hard facts to die. It is almost as if they hope yet to detect life where there is none.

The ancient journals, too, have a strange, nostalgic fascination. It is a privilege to lift the veil and listen, even if rather indistinctly, to men like August Krogh or Lindhard or Yandell Henderson, and how interesting it is to find that the views some of my older contemporaries express today found origin in ideas and concepts that they lived with, as only a scientist worrying out an idea can live, perhaps thirty years ago.

* * *

My partner, who has only been two years in general practice, remarked the other day that really important statements by patients or their relations are often made on the doorstep on departure.

My mind must have registered this too, without having put it into words, for it at once accepted the truth of the observation. If I needed confirmation it came at once. The next day as I was leaving the house of a man with depression and dyspepsia, who refused to own up to any worries or reasons for nervous tension, a married daughter saw me to the door and literally on the doorstep said, "You know, my sister wants to get engaged, but father so dislikes the idea of losing his youngest daughter that he won't even meet the young man."

The incident that had struck my partner so forcibly was his visit to a child with the mildest of sore throats. As he was leaving the mother said, "By the way, doctor, my husband is coughing up blood, but he won't tell you himself."

* * *

A colleague practising in a Yorkshire mining town describes his most embarrassing moment. Called in to give a supporting certificate for cremation, he did his duties quietly and speedily and expected that the undertaker would be equally circumspect, and would forward the prescribed fee later on.

A few days later he stood to attention in the High Street as a funeral procession crawled by. Suddenly the leading vehicle swerved across to where he stood and a hand poked out towards him. "Your £2, doctor—saves a stamp," said the top-hatted and black-coated driver, who then resumed his place at the head of the dignified procession.

Letters to the Editor

THYMECTOMY AND MYASTHENIA GRAVIS

SIR,—There are many arguments against the likelihood of thymectomy benefiting sufferers from myasthenia gravis. The only justification for attempting the surgical experiment was the enlargement of the gland in some patients and the presence of a " thymoma " in a number of others. It has to be admitted, however, that a majority of patients have a thymus that is normal in every respect, and, again, a thymoma does not necessarily lead to myasthenia. Removal of the thymus is followed by no symptom whatever, no recognisable syndrome of hypothymism. This suggests surely that the function of the thymus, if any, is duplicated by other organs and that this gland is comparable in this respect to the spleen rather than to any known endocrine gland.

When we come to the results of thymectomy, recently assessed by Simpson [1] and discussed in your excellent leading article of Sept. 6, we find some very puzzling features. The operation benefits women, but probably not men. The worse results are to be expected when the most abnormal glands, the thymomas, are removed, although an excellent result is sometimes seen in this category of patients and indeed often follows removal of apparently normal glands. The chances for the myasthenic to remain in status quo, operation or no operation, are about the same. If men, children, and the bearers of tumours are excluded and assessment is focused on a special class, women between 16 and 35 years old, then we find a distinct advantage for surgery.

My knowledge of the statistical method does not allow me to judge how far it is fair to separate and select groups of patients in this way. Assuming the favourable response of some young female patients to be proven, I would like to refer again to a suggestion I made some years ago.[2] I said then, " Can it be that myasthenia gravis is a label covering a number of disorders of the myoneural junction? Every functional unit of the neuromuscular system has its own varied pathology. . . . Is it not, a priori, likely that the myoneural junction . . . can be impeded in more ways than we know? "

Suppose that an enterprising surgeon, fifty years ago shall we say, had decided for splenectomy in every obscure case of anæmia, as this organ was often known to be enlarged; would he not have had some remarkable results —for instance, in a group of young subjects with a familial incidence of anæmia?

London, W.1. L. P. E. LAURENT.

THE NATURE OF THE INSULIN-ANTAGONIST ASSOCIATED WITH PLASMA-ALBUMIN

SIR,—We have recently shown that the inhibitor of insulin in the plasma of diabetic patients is associated with the albumin fraction. Furthermore it was shown that albumin from normal subjects also has an inhibitory action.[3] These studies gave no indication of whether such an inhibitory activity was due to the albumin per se or was due to a substance associated with it. We now wish to present evidence that the latter is the case.

Effect of Hypophysectomy

Three hypophysectomised patients have been studied. Two of the patients had carcinomatosis and had their pituitary ablated by transnasal implants of yttrium-90 into the sella turcica. These patients were cortisone-dependent. The third patient was diabetic and the pituitary gland was removed by surgery, which was easy and complete. Albumin was prepared by the trichloroacetic-acid/ethanol method from the plasma of these patients and tested for insulin antagonism by the rat-diaphragm technique as described in our last paper.[3] The plasma-albumin fractions from all these patients had no demonstrable antagonistic activity. The albumin fraction in each case was tested at least twice. The results which have been taken together are shown in the accompanying table. In one case it was possible to determine the activity of the albumin fraction before operation and as expected this fraction was inhibitory.

ACTION OF ALBUMIN FROM NORMAL, HYPOPHYSECTOMISED, AND DIABETIC SUBJECTS

Fraction	Mean glucose uptake above basal level ± standard error of the mean (mg. per 100 ml. per 10 mg. diaphragm)	
	Buffer + 1000 microunits per ml. insulin	Fraction in buffer + 1000 microunits per ml. insulin
Normal albumin (3·5–5·5%)	11·43 ± 0·62 (6)	0·50 ± 0·48%
Hypox. albumin* (4%) ..	11·85 ± 0·68 (8)	11·43 ± 0·80 (8)
Diabetic albumin (1·25%)	12·32 ± 1·04 (4)	3·55 ± 0·67 (4)
Diabetic albumin through column (1·25%)	13·12 ± 0·65 (6)	12·58 ± 1·28 (6)

No. of observations in parentheses.
*Hypox. albumin represents albumin isolated from the plasma of hypophysectomised patients.

Removal of Activity on Columns of Cellulose

Albumin from diabetic patients (300 mg.) was prepared, with the activity previously described,[3] dissolved in 4 ml. of borate-phosphate buffer, and passed through a column (40 cm. × 1·5 cm.) of cellulose.[4] The protein was eluted with buffer and a total of 150 ml. of buffer was collected, the eluent extensively dialysed and the protein freeze dried. When the activity of this protein, which was electrophoretically identical with albumin, was tested, the original activity against insulin was found to have been removed by passage through the column. The results are shown in the table. A similar result was obtained when 750 mg. of normal albumin was passed through a column under similar conditions.

Together, both these lines of evidence indicate that the activity of the albumin fraction from normal subjects and diabetic patients against insulin is not due to albumin per se. The results of hypophysectomy indicate that the antagonistic activity is related, possibly indirectly, to the pituitary gland. This gland may not be solely responsible, however, as is suggested from studies on experimental diabetes in animals. Thus in depancreatised cats the presence of insulin antagonism in the plasma is dependent both on the presence of the pituitary gland and on adrenalcortical steroids.[5] These results are in accord with those of Luft et al.[6], who showed that the insulin requirements of diabetics who had been subjected to hypophysectomy fell as the result of the operation.

We should like to thank Prof. Russell Fraser and Dr. J. D. N. Nabarro for allowing us to study patients under their care, the Medical Research Council for a grant for scientific assistance, and Boots Pure Drug Company for supplies of recrystallised insulin.

Department of Medicine, Postgraduate Medical School of London, W.12. J. VALLANCE-OWEN
ELIZABETH DENNES

Courtauld Institute, Middlesex Hospital, London, W.1. P. N. CAMPBELL.

1. Simpson, J. A. *Brain*, 1958, **81**, 112.
2. *Brit. med. J.* 1949, ii, 814.
3. Vallance-Owen, J., Dennes, E., Campbell, P. N. *Lancet*, 1958, ii, 336.
4. Campbell, P. N., Stone, N. E. *Biochem. J.*, 1957, **66**, 19.
5. Vallance-Owen, J., Lukens, F. D. W. *Endocrinology*, 1957, **60**, 625.
6. Luft, R., Olivecrona, H., Ikkos, D., Kornerup, T., Ljunggren, H. *Brit. med. J.* 1955, ii, 752.

SKIN TRANSPLANTATION IMMUNITY IN RELATION TO HYPERSENSITIVITY

SIR,—Reading, with appreciation, the preliminary communication of Sept. 13 by Professor Medawar and his colleagues, I was left uncertain as to the nature of the material obtained from the cells expressed from the lymphoid tissue of the recipient animal and injected in the "direct reaction"—presumably mitochondria and microsomes (R.N.A. granules), amongst other things.

Professor Medawar at one time produced evidence which indicated that there were tissue antigens in cell nuclei. On general principle, it seems improbable that tissue antigens or, to use Loeb's more descriptive term, differentials are the exclusive property of any particular cell extract or fraction. More likely it is an attribute pervading all living macromolecular systems in the higher animal form and resides in characteristic molecular configurations. The proteins, with a choice of over twenty aminoacids offering an infinite number of positions for all the possible side-groups and linkages, could provide a sufficient range of molecular pattern for all tissues, individuals and species. One wonders, therefore, if elaborate procedures and processing of living tissue adds anything to the problem of homograft reaction.

Department of Anatomy,
University of Glasgow. G. M. WYBURN.

SPHINCTER AND HIATUS

SIR,—An interesting aspect of the hiatus-hernia problem, so far not mentioned in your review of this fascinating subject, is whether or not so-called "sliding" hiatus hernias commonly slide.

Belsey [1] has stated that they rarely slide to and fro through the hiatus, the radiological appearances being an illusion. However, so long as it is generally accepted that a hernia may come and go spontaneously, the radiologist has an excuse for not demonstrating the lesion regularly when it is present, and moreover will tend to be preoccupied with manœuvres designed to promote reflux and/or herniation. It is a common experience that repeated barium examinations are at present necessary in a proportion of cases.

Rejecting this assumption immediately puts the radiologist on his mettle to improve the present unreliable technique. In this respect the image intensifier offers hope for the future; with its use gastric-type mucosal detail may often be clearly seen above the diaphragm as the barium bolus passes, even in the erect position.

Supposing that the hernial pouch is permanently fixed above the diaphragm and that the pressure within it approximates to that within the intra-abdominal stomach,[2] then support for the action of the external mechanisms acting at the hiatus in preventing reflux into the pouch during barium-meal examination, is provided by the following simple experiment. If a baby's feeding-bottle is inverted with the neck of the teat partially constricted (by compression or angulation), then the bulb will not fill completely with fluid because an air-bubble is present. In the case of a hiatus hernia, this mechanism would probably act as a complete or partial air lock, the air being prevented from escaping upwards by the alleged internal sphincter or by a more diffuse contraction of the lower œsophagus, as mentioned previously.[3] Complete occlusion of the neck of the hernia at the hiatus would be unnecessary, which would account for the rather unimpressive pressure changes found here.

Belching would tend to lose the air and so promote reflux. Donnelly [4] has related the formation of a hiatus hernia and reflux symptoms to this habit.

Southmead Hospital,
Westbury-on-Trym,
Bristol. E. A. W. HOUGHTON.

BREAKING UP THE MENTAL HOSPITAL

SIR,—Although broadly agreeing with the views expressed by Dr. Russell Barton (Sept. 13), we feel that the topic is of such importance that it deserves further ventilation.

Anybody who studies the history of psychiatry will find that from time to time during the last 100 years the same ideas on treatment have been dressed up in new clothes and put forward as a sure solution of the problems confronting mental hospitals. This applies particularly in the field of *administrative* psychiatry where we now hear repeated pleas for the doors to be thrown open and the patients discharged to the tender and loving care of their relatives. We also find a resurgence of the idea of community care, domiciliary treatment, and indeed complete abolition of the mental hospital.

With the *medical* problem of psychiatry in its present state of flux, it is as well to view any of these new advances with a critical eye. For example, nowadays the old concept of the hospital farm, where chronic patients could work, is considered outmoded and many hospital farms have been closed as uneconomic. This idea has now been replaced by the plea for factories to be established in mental hospitals. Are they to be more economical? Some years ago large observation wards attached to general hospitals were instituted as an administrative solution to many problems in industrial cities such as Glasgow and Manchester. Today this idea is discredited because these wards have failed to cope with the disposal of chronic cases. Nevertheless, psychiatric departments in the general hospitals are suggested as a panacea against institutionalisation by some reformers. The situation would not seem to be very dissimilar to that which prevailed in the treatment of tuberculosis before the advent of modern effective chemotherapy. Some saw the solution in extensive village settlements, others through the provision for outpatient dispensaries, &c.; in fact, the real advance has had to wait the advent of an effective medical rather than administrative treatment. Administrative changes in psychiatry are required and may indeed be helpful; but we should like to make a plea for a degree of self-criticism which is not often apparent in those who conduct these so-called new experiments.

We disagree with the views expressed in Dr. Barton's article about institutional "neuroses." The features of apathy and indolence so often seen in chronic schizophrenics are essentially a product of the disease itself and, like aggression and hostility, not infrequently seen in schizophrenics who have lived outside a hospital all their lives, as we tried to demonstrate in our description of the chronic patient in India.[5]

The enthusiastic and sometimes incautious discharge policy of some hospitals can indeed have tragic repercussions on the family.

A case recently seen by one of us had passed through the hands of a mental hospital near London where a man in his fifties had been under care and treatment for the past ten years. The hospital discovered that the patient had a sister in her seventies living near Birmingham and wrote to her that

1. Belsey, R. in Modern Trends in Gastro-enterology. London, 1952.
2. Atkinson, M., Edwards, D. A. W., Honour, A., Rowlands, E. W. *Lancet*, 1957, ii, 1138.
3. *ibid.* Sept. 6, 1958, p. 525.
4. Donnelly, B. *Brit. J. Radiol.* 1953, **26**, 441.
5. Mayer-Gross, W., Cross, K. W., Harrington, J. A., Sreenivasan, U. *Lancet*, 1958, i, 1265.

the patient was now well and was to be discharged under her care; no other preparations for the transfer were made. The results were disastrous; the still psychotic patient nearly drove his sister to a breakdown and had to go into hospital in Birmingham. This case is by no means an isolated example, and we frankly admit that we have seen equally bad effects on the family of some of our own patients we have attempted to discharge from hospital.

Psychiatrists battling with a human problem of the greatest practical difficulty are certainly not immune from self-deception; but neither are experts in social medicine, nor our Great Planners and Medical Politicians. A lack of critical evaluation of what we are trying to do often leads to an overactivity in the wrong direction and to a repetition of past errors.

Uffculme Clinic,
Moseley, Birmingham.

W. MAYER-GROSS
J. A. HARRINGTON.

SIR,—The letter from Dr. Russell Barton raises a number of relevant questions.

We know that some of our discharged patients have entered other hospitals, just as we admit patients who have been treated elsewhere. Nevertheless, it is our impression that more patients move into our area than out of it. This impression is strengthened by our social worker's reports and is in keeping with the fact that schizophrenic patients tend to be found in excess in the central areas of towns.[1 2]

I am indebted to Dr. Walk of Cane Hill Hospital, who has allowed me to see some figures he has collected from the Coroner's courts of South London. These show that in 1956 and 1957 the number of ex-patients from Banstead who committed suicide was less than half of that for the other comparable hospitals.

Contrary to Dr. Barton's statement, we do not know of any mental hospital which is willing to take patients from our area. Moreover, we have had referred to this hospital a number of patients from outside our area. They were referred to us because of our policy of active treatment in an optimistic atmosphere.

We are, of course, particularly concerned that discharged patients should not cause distress in their homes. Apart from a general awareness of this risk, we have had a research scheme running for nearly three years, which is concerned with the social problems of schizophrenic mothers. This group was chosen because it was thought it would highlight the problems of patients returning to the community. It is apparent that all these patients have difficulties on leaving hospital—sometimes severe. In general however, once overt symptoms have been treated, the longer the patient is away from home, the greater the difficulties the whole family will experience when attempts are made to re-unite them. Once the optimal time has passed, families tend to organise their lives without the absent member.

I entirely agree that institutional neurosis can develop in small wards as readily as in large, and the most important factor in curing this condition is the spirit which animates the staff. It is difficult to see how a mental hospital can provide full after-care facilities without becoming unwieldy. I would agree with Dr. Barton however if he means that such facilities in the community should be supervised from the mental hospital.

Banstead Hospital,
Sutton, Surrey

A. A. BAKER.

1. Faris, R. E. L., and Dunham, H. W. Mental Disorders in Urban Areas. Chicago, 1939.
2. Hare, E. J. *J. ment. Sci.* 1956, **102**, 349.

INDUSTRIAL MEDICINE AND GENERAL PRACTICE

SIR,—I should like to support Dr. Keatinge (Sept. 6) in questioning Lord Taylor's contention that "a large part of industrial medicine is neither more nor less than general practice". The latter is freely assumed by lay people to be the only form of medical activity (other than hospital work) undertaken by doctors, and when an eminent authority emphasises this feature, it makes it increasingly difficult for industrial medical officers to persuade managements and employees that this is not the case.

In discussing broad issues generalisations are a necessary evil, but I think few will disagree with the statement that the general practitioner mainly directs his efforts to the detection and treatment of disease while the industrial medical officer is mainly concerned with the *relationship* between disease (or disability) and occupation. This relationship may find expression in three ways:

(1) *Causation:* disease or disability directly of industrial origin.

(2) *Aggravation:* where conditions of work make worse a disease or disability already present.

(3) *Interference:* where the disease or disablement interferes with the ability of the employee to do his work.

These aspects of the relationship between disease and occupation may appear singly or together. Whatever is the case, the efforts of the industrial medical officer are directed to removing, ameliorating, or otherwise adjusting the relationship. Ideally the relationship should exist in theory only, and preventative medicine truly would have been done.

If this simple conception of an industrial medical officer is kept in mind then there will be no confusion as to whether he "practises generally".

Before I am attacked on all sides I should like to add that the provision of emergency treatment for accident and illness is a vital part of his work but it should in no way be regarded as the paramount reason for his existence in industry.

Medical Department,
Stewart and Lloyds,
Newport, Mon.

G. THOMAS.

TRIALS OF CONTRACEPTIVES

SIR,—This Council is trying to organise clinical trials to test the efficacy of existing methods of contraception. We are also hoping to try modifications of these methods and ultimately, we hope, entirely new methods will be tested in the same way.

To establish any new method of contraception needs volunteers who are willing to run a reasonable risk of becoming pregnant, and who are also likely to be fertile. We have in fact two groups of trials running at present:

Group 1, in which the volunteers use the method for from 3 to 12 months and then prove both its effectiveness and their fertility by becoming pregnant; and group 2, in which volunteers use a method for about a year, being prepared to run the risk of its failing but not being prepared to undertake pregnancy. There is also a third trial in which patients are medically seen and examined at a special clinic session in London. Group 1 and 2 patients are not seen unless the patient-volunteer specifically wants to be seen.

In view of our lack of accurate figures about the effectiveness of modern contraceptive methods and because of the importance of this problem both to individual families and to world population trends we feel that the trials are of vital importance.

If any of your readers can put us in touch with volunteers (who should write to the medical secretary at this address) we would be most grateful.

G. I. M. SWYER
Chairman
H. B. WRIGHT
Secretary,
Technical Subcommittee.

Council for the Investigation of Fertility Control, 64, Sloane Street, London, S.W.1.

HÆMORRHAGIC PLEURAL EFFUSION AS A MANIFESTATION OF SCURVY

SIR,—Dr. Rozner and Dr. Lloyd (Aug. 23), in their interesting article on scurvy, quote Lind (1753) for an early description of pleural involvement. I should like to call attention to Jacques Cartier's *Brief Recit* of 1545 in which he describes the postmortem findings of a case of scurvy in Canada in the year 1535.

"Because of our ignorance of the disease, the captain had the body opened to obtain whatever knowledge of it might help to preserve the rest of us if possible. The heart was found white and wrinkled, with nearly two quarts of reddish, date-coloured water about it. The liver was healthy but the lungs were all blackened and mortified and all the blood had collected above the heart, for, when the body was cut open there issued from above the heart a large amount of dark, putrified blood. The spleen, for two finger breadths near the backbone, was likewise a little affected, as if it had been rubbed on a rough stone. These facts having been noted, one thigh was cut open and found very black outside but with fairly healthy flesh inside." (From the translation of Prof. Jean L. Launay.)

J. M. PARKER
Pharmacologist.

Charles E. Frost & Co., Montreal.

CONTROL OF THE COMMON COLD

SIR,—Over a period of years, it was noted that quite unexpectedly good results were being given by prophylactic autogenous vaccines in the prevention of the common cold. It seemed reasonable to assume that the function of the virus was essentially that of a starting handle, most of the later and debilitating symptoms being due to the patient's own nasopharyngeal bacteria which became out of hand as a result of the general depression due to the virus.[1]

If so, a similar result should be obtainable by short-term local antibiotic therapy at the start of the symptoms, thus depressing the activity of the bacteria to correspond to the general depression of the patient. A series of experiments was therefore carried out during the winter of 1956–57. The result confirmed expectations, in that use of the appropriate antibiotic at the onset considerably reduced the number of fully developed colds.[2]

During the winter of 1957–58, a further trial was made on exactly the same lines as that of the previous winter, essentially as a check to ensure that the highly promising results achieved were not due to chance in any way. The results are given in the accompanying table.

The proportion of volunteers with prodromal symptoms who went on to a full cold was again much lower in the treated than in the control group. As in the previous series, lateness in reporting prodromal stages proved disadvantageous, but this trial was intended to be a practical one and the figures therefore include all comers.

From October, 1957, until May, 1958, 1120 volunteers were divided into two groups. Of these, 838 received short-term antibiotic treatment when they felt a cold beginning, and 282 received an inert tablet. In the treated group, prodromal stages numbered 304 (36·3%) of which 52 (17·1%) went on to full colds. In the control group, the prodromal stages numbered 121 (42·8%) of which 64 (52·9%) went on to full colds—i.e., 6·2 colds per 100 volunteers in the treated and 22·7 per 100 in the control group.

Allowing for the fact that latecomers (i.e., those reporting prodromal stages after a day or two) were accepted in 1957–58 and largely refused in 1956–57, these figures strongly support the findings of the previous year—4 colds per 100 in the treated and 26 per 100 in the controls. For 304 volunteers where such assessment was possible the figure for 1957–58 worked out at 4·8%.

The fact that the findings during 1957–58 show such a strong resemblance to those of 1956–57 is evidence that the conclusions put forward, and probably the assumption on which they are based, are correct. In that case, the following points arise:

(1) *Chronic cold sufferers.*—The method of choice here is the autogenous vaccine, giving active immunity. A short course of minimal oral antibiotic may if necessary be given to prevent development beyond the prodromal (virus) stage, but this should not be necessary once immunity has developed. A sensitivity test can be recorded when the vaccine is made in case it is required. Incidentally, such patients as have had two courses of vaccine appear to have developed a lasting immunity, none ever having been given a third.

(2) *The "casual" cold.*—This does not warrant a vaccine and should respond to oral antibiotics on the lines indicated. In industry, where a medical centre is available, sensitivities can easily be recorded in the early autumn, for use throughout the ensuing winter. There is, of course, nothing to prevent

1. Ritchie, J. M. *Lancet*, 1958, *i*, 615.

2. Ritchie, J. M. *ibid.* p. 618.

NUMBER OF VOLUNTEERS AND INCIDENTS IN EACH GROUP

—	Works I (aeroplane parts)		Works II (feeding-stuffs)		Works III (rubber tyres, &c.)		Total	
	A	K	A	K	A	K	A	K
No. of:								
Volunteers (V)	534	182	228	75	76	25	838	282
Colds (a)	31	39	8	14	13	11	52	64
Improved only (b)	14	2	2	—	—	—	16	2
Prodromal only (c)	118	34	63	17	55	4	236	55
Incidents (a+b+c)	163	75	73	31	68	15	304	121
a/a+b+c	31/163	39/75	8/73	14/31	13/68	11/15	52/304	64/121
%	19·0	52·0	10·9	45·2	19·1	73·3	17·1	52·9
c/a+b+c	118/163	34·75	63/73	17/31	55/68	4/15	236/304	55/121
%	72·4	45·3	86·3	54·8	80·9	26·7	77·6	45·5
a+b+c/V	163/534	75/182	73/228	31/75	68/76	15/25	304/838	121/282
%	30·5	41·2	32	41·3	89·5	60·0	36·3	42·9
a/V	31/534	39/182	8/228	14/75	13/76	11/25	52/838	64/282
%	5·8	21·4	3·5	18·7	17·1	44·0	6·2	22·7

A = no. of volunteers reporting incidents who received antibiotics.
K = controls, receiving inert tablets.

practitioners doing the same with patients, but as these do not usually report at the beginning of a cold, the early opportunity is apt to be missed. It has been found that, although there is a considerable degree of constancy in the mouth flora, it is better to repeat the sensitivity test each autumn.

(3) *Influenza.*—Many practitioners have noticed that treating some early cases of influenza with systemic antibiotics, on purely empirical grounds, appears to have reduced the incidence and severity of complications. It is perfectly logical to assume that, if the cold virus is essentially a starting-handle, the influenza virus may be the same, albeit on a different scale. The continued prophylactic use of systemic antibiotics may lead to the production of resistant bacteria and is therefore to be condemned, but their administration for a few days in an emergency like an imminent attack of influenza is open to no such objection. As the result of a sensitivity test can be read after overnight incubation, there is no reason why the antibiotic appropriate to the patient's nasopharyngeal flora should not be used in an attempt to reduce the effects of bacterial invasion, even in cases of influenza.

Public Health Laboratory, Birkenhead. J. MORRISON RITCHIE.

HÆMORRHAGIC LESIONS DUE TO STAPHYLOCOCCAL TOXIN

SIR,—The production of hæmorrhagic consolidation of the lungs, in mice, using filtrates of staphylococcal cultures, reported by Professor Ogasawara and Dr. Tanaka [1], is an important observation. The experiments reinforce the suggestion that fatal hæmorrhagic staphylococcal pneumonia, in man, is due to the production of staphylococcal toxin in the colonised lungs.[2] Furthermore they re-emphasise that the rapidly lethal effect of staphylococcal toxin in experimental animals can be prevented by antitoxin; we hope this will encourage further trials of the treatment of acute staphylococcal toxæmia, in man, with staphylococcal antitoxin.[3]

It might, however, be unwise to risk aggravating the characteristic systemic hypotension of staphylococcal toxæmia by the use of tetra-ethyl ammonium compounds or by chlorpromazine until there is further evidence of the efficacy of these drugs in protecting the pulmonary circulation from the acute pressor effects of staphylococcal toxin.[4]

Department of Pathology, University of Cambridge. G. A. GRESHAM
M. H. GLEESON-WHITE.

COLOUR INDEX IN NORMAL SUBJECTS

SIR,—Dr. Pooley (Sept. 13) gives values for the colour-index to the nearest 0·01. Such supposed accuracy is surely without meaning, for to be able to estimate the colour-index to within a range of 0·01 the hæmoglobin must be estimated to within ±0·25%, and the red cells to within ±12,500 per c.mm.

Even the more rational calculation within 0·05 requires a hæmoglobin ±1·25% and red cells ±62,500 per c.mm.—an accuracy beyond that of a routine hospital laboratory.

Briggs and Allington, using the M.R.C. photometer, found a standard deviation of 4·5% for successive hæmoglobin estimations on the same subject, and I have seen a teaching hospital laboratory vary by as much as 10%.

I therefore doubt whether there is much practical value in reporting the colour-index to a second decimal place, using laboratory methods at present available.

Department of Pathology, Royal Infirmary, Blackburn. KEITH HORSFIELD.

1. *Lancet*, Sept. 13, 1958, p. 589.
2. Gresham, G. A., Gleeson-White, M. H. *ibid.* 1957, i, 651.
3. Gresham, G. A. *Brit. J. clin. Pract.* 1958, **12**, 247.
4. Burnet, F. M., Kellaway, C. H. *Med. J. Aust.* 1930, ii, 295.

CHILDREN IN HOSPITAL

SIR,—It is difficult to criticise constructively the long letter of Mr. Herzog in your issue of Sept. 6, as there is so much with which a psychiatrist can agree. I am sure he is right when he implies that patients over five years, and certainly those over eight years of age, can do with weekly or even less frequent visiting. This is especially true when the community atmosphere is highly developed and when all the adults surrounding the children are able to make good and happy relationships that are warm and permissive, not cold and punitive, as still happens in some children's wards.

It is, however, one of the disadvantages of boarding schools that they weaken family relationships, at least in the pre-adolescent. It is imperative that we constantly remember that family loyalty is something far more precious and important than group or national loyalty.

With regard to the under fives, and especially to those of two and three years of age, frequent and if possible daily visiting is vital to the proper development of their personality and emotional stability. One recognises that at times this may be very difficult and require great sacrifice on the part of parents, and that in some cases it is impossible. However, it is our duty to see that parents who *say* they cannot visit frequently are, in fact, not unaware of the intense suffering of small children separated from their parents. They should be helped to be made aware of the emotional needs of those small children and then perhaps they will realise that making tea for their husbands coming home from work is not in itself a good reason for staying away. Any husband worth his salt can get his own evening meal.

Of course, it is not just the frequent contact with parent and child that is important but the depth and quality of their unconscious non-verbal relationship. This cannot, of course, be produced by ministerial directives on visiting. Where it is deficient it can only be produced by analytically orientated group or individual discussions with parents. Sometimes, of course, so malignant are the unconscious forces in a mother's personality that this happy relationship can never be produced.

Would not Mr. Herzog agree that the child in the film *A Two-year-old Goes to Hospital* suffered? Would he not agree that the clinging and demanding behaviour after that child returned home is at the very least distressing to parent and child? Surely it is our duty to minimise all suffering to the utmost of our limits. For those who have eyes to see the film is quite conclusive. A recent letter in the *Manchester Guardian* clearly demonstrated the after-effects of a prolonged stay in orthopædic hospitals, which were in essence a permanent and more severe form of those demonstrated by the film.

The remark that disturbed me most in Mr. Herzog's letter was that " crippled children stand out because of their quiet, non-complaining behaviour ". By writing such a statement he has unwittingly vindicated the work of Dr. Bowlby and others. Quiet passivity is the depressive picture seen in those who have suffered severely from prolonged emotional deprivation and is particularly seen in many displaced persons who have for years been emotionally starved in concentration camps, a sign therefore of serious maladjustment rather than good adjustment.

Might I suggest that Mr. Herzog and those who think like him could perhaps find time to study more closely with their psychiatric colleagues the sometimes hidden and subtle effects of hospitalisation.

Carlton Hayes Hospital, Narborough, nr. Leicester. H. B. KIDD.

SIR,—I am delighted to read that hospitals are not so bad for children after all. I congratulate Miss Stephen and Dr. Whatley (Sept. 20) on their most enlightened approach to this question.

I suppose we are an enlightened isolation hospital in that daily visiting of children is allowed, together with extra visiting as indicated.

Personally I have noted little difference in the behaviour of children. The majority settle down as they always did. A few fret and fume, but nine times out of ten they are only children of elderly or anxious parents.

As Miss Stephen and Dr. Whatley say, some have actually benefited morally and psychologically from their stay, in particular backward children and those from homes where there is parental discord.

Those that are discharged against medical advice do not amount to more than 0·01% of all admissions.

Ilford Isolation Hospital,
Chadwell Heath, Essex. I. M. LIBRACH.

THE MEDICAL SOCIETY OF LONDON

Sir CECIL WAKELEY, president of the Medical Society of London, writes:

"I am writing to crave your assistance in helping this old Medical Society of London to obtain pictures of former presidents. We have almost a complete list of presidents of this society since its foundation in 1773, but we have a few gaps over the years. I should be very grateful if any of your readers can help the society by loaning pictures of any of the following:

John Millar, M.D., 1773	George Pilcher, 1842
George Edwards, M.D., 1779	Theophilus Thompson, M.D., F.R.S., 1844
George Pinckard, M.D., 1811	Walter Cooper Dendy, 1846
Thomas Walshman, M.D., 1817	Edward Headland, 1854
David Unwins, M.D., 1821	Francis Hird, 1857
William Shearman, M.D., 1823	William Hughes Willshire, M.D., 1858
John Burne, M.D., 1831	Francis Sibson, M.D., F.R.S., 1862
John Whiting, M.D., 1835	Peter Marshall, 1869
Thomas Egerton Bryant, 1837	John Cockle, M.D., 1879
Leonard Stewart, M.D., 1839	

I am very keen to see the completion of this permanent record of photographs of all the past presidents."

Diary of the Week

SEPT. 28 TO OCT. 4

Tuesday, 30th

ROYAL STATISTICAL SOCIETY
5.30 P.M. *Medical section.* (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. J. P. M. Tizard: Prevalence of Mental Defect.

Wednesday, 1st

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.15 P.M. *History of Medicine.* Sir Eric Riches: A Manuscript of Benjamin Collins Brodie's Surgical Lectures—with Some Notes on the History of Stricture and Stone.
8 P.M. *Surgery.* Dr. B. Marden Black (Mayo Clinic, Minnesota), Mr. Vaughan Hudson: Present-day Views on the Treatment of Thyroid Conditions (other than Cancer).

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Sir Russell Brock: Surgical Treatment of Pulmonary Stenosis.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. R. W. Riddell: Fungi as Saprophytes and Parasites.

MANCHESTER MEDICAL SOCIETY
5 P.M. *Medicine.* (Medical School, University of Manchester.) Dr. R. W. Luxton, Dr. Deborah Doniach: Hashimoto's Disease.

Thursday, 2nd

ROYAL SOCIETY OF MEDICINE
5 P.M. *United Services.* Dr. A. M. Joekes: Hæmodialysis in Renal Failure and Some Points in the Diagnosis of Acute Renal Failure. Group-Captain R. C. Jackson: Experiences with the Kolff Twin Coil Artificial Kidney. Dr. J. E. Scott: Biochemical Aspects of Hæmodialysis.
8 P.M. *Neurology.* Dr. Hugh Garland: Endogenous Hypoglycæmia. (Presidential address)

ASSOCIATION OF CLINICAL PATHOLOGISTS
2 P.M. (Royal College of Surgeons, Lincoln's Inn Fields, W.C.2.) Opening of three-day meeting.

Friday, 3rd

ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Anæsthetics.* Dr. H. J. V. Morton: Demonstration and Deception by Diagram. (Presidential address.)

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Dr. Norman Hulbert: Blood Disorders in Association with Ear, Nose, and Throat Diseases.

Notes and News

AN ANATOMICAL LANDMARK

IT might be thought that when a new book is described by a reviewer as "not wanted", "low", and "unscientific in tone", it could have little hope of success. And when its publisher goes out of business and its young author dies soon after preparing a second edition, the work must surely disappear. Yet Mr. Henry Gray's *Anatomy*, which suffered this vile concatenation of events, has survived; and today it prospers increasingly, as Mr. William Longman was able to relate at a dinner given in Stationers' Hall, London, on Sept. 18 to celebrate the centenary of its first appearance. Prof. T. B. Johnston, who has seen "Gray" through nine editions since 1930, ruefully admitted that fifty-seven years ago, when he traded his "Liddell and Scott" for "Gray", he felt at first that he had made a bad bargain. Anyone buying the centenary edition, though he must dig deep in his pocket, is less likely to be seized with regret than with gratitude to Professor Johnston and his two associates, Professor D. V. Davies and Professor Francis Davies, for keeping their charge so free from the marks of age. Textbooks may come and go; but "Gray", it seems, remains for ever, a welcome landmark in a shifting landscape.

OLD PEOPLE WAITING FOR BEDS

IN 1951 the Hospital Personal Aid Service for the Elderly was set up by King Edward's Hospital Fund to visit in their homes old people who are awaiting admission to hospital. The service visits only at the request of the hospital staff, and in their report for 1957 they say that during the year they visited 1765 old people on behalf of 15 hospital management committees. On their visits the caseworkers of the service collect information about the patients' home circumstances, which is a useful guide to the hospital both in assessing priority for admission and later in arranging for discharge. The visits also ensure that waiting-lists are kept up to date and that the names of patients who no longer want a bed are removed. The service is able to report that since it began its work in 1952 the percentage of patients who have to wait over two months for a bed has fallen from 23 to 2, and that in 1957 66% of their patients were admitted within a week. The address of the service is New Cross General Hospital, Avonley Road, London, S.E.14.

FACIAL ECZEMA IN NEW ZEALAND SHEEP

AN important advance in the knowledge of the ætiology of facial eczema has been reported by Dr. C. P. McMeekan from the Government Animal Research Station at Ruakura, near Hamilton, where the elusive toxic factor has been identified with the fungus *Stemphylium botryosum*.

The disease (writes our New Zealand correspondent) affects mainly sheep, and is almost entirely limited to the North Island, though cattle are also affected and the guineapig can be used for laboratory studies. Jaundice and sores on exposed parts of the body—especially around the face—are attributed to liver damage and the circulation of photosensitive breakdown products. The liver lesion is essentially a cholangitis affecting the smaller ducts, and when severe can lead to obliteration and fibrosis.

The dangerous time of year for outbreaks of facial eczema is autumn, when warm rains encourage the growth of fresh young grass—particularly in the ryegrass area. As yet the only useful palliative measure has been to crowd sheep together to prevent their getting too much "toxic" grass; and warnings are issued each season when conditions are thought to be conducive.

Though many people—farmers as well as scientists—have incriminated a fungus or other live product as the causal agent, there has previously been no proof of such a theory. For many years research has been predominately chemical and aimed at identifying a toxic substance in grass.

The present success followed the observation by a farmhand that a fine cloud rose from his mower when he was cutting

the "toxic" grass. He found some mycelial growth at the roots of the grass, and later scraped a fine black deposit off the blades of the mower. These both gave positive empirical "beaker" tests for toxicity, and cultures of the fungus have yielded an extract which reproduces facial eczema in guinea-pigs and lambs.

Much remains to be done. In particular it is not known why the fungus is widespread, although the disease is not. But the team of four special chemists and pathologists from Great Britain who will reach New Zealand early next year to carry out further research will now have a much more promising task.

Royal Society of Tropical Medicine and Hygiene

The opening meeting of the session will be held at 26, Portland Place, London, W.1, on Thursday, Oct. 16, at 7.30 P.M., when Sir Philip Manson-Bahr will give the first Manson oration. He will speak on the March of Tropical Medicine during the last Fifty Years.

St. Mary's Hospital, Manchester

On Friday, Oct. 31, at 4.30 P.M., at the Clinical Sciences Building, York Place, Manchester, 13, Prof. A. M. Claye will give the Lloyd Roberts lecture. His subject will be The Teaching of Obstetrics—New Edition.

A New Teaching Hospital

The Minister of Health has announced that he has authorised the Board of Governors of the United Cardiff Hospitals to appoint architects for the new hospital and medical school to be built at Cardiff. He understands that the board intends to hold an architectural competition.

A City Sponsors Research

The Mayor of New York has announced (*New York Times*, Sept. 18, 1958) the creation of the New York City Health Research Council with an initial income, from tax appropriation, of $600,000. The council is to sponsor public and private research, and priority is to be given to problems of ageing; childbirth and infant care; mental illness; accidents; heart-diseases; environmental hazards, including air pollution and radiation; and patient-care.

New Surgical Block at Guy's

On Sept. 19 Lord Nuffield, president of Guy's Hospital, London, laid the foundation stone of its new surgical block.

The 11-storey building will have 10 operating-theatres, 14 wards, and maternity, radiotherapy, and casualty departments. In all it will have 378 beds. It is hoped that it will be ready in 1960. The block will cost about £2¼ million.

North Western Thoracic Society

This society will hold its first meeting of the session on Thursday, Oct. 16, at 5 P.M., in the Clinical Science Buildings, York Place, Manchester, when Dr. Robert Coope will give a presidential address on Sundry and Manifold Changes.

British Institute of Radiology

The annual congress and exhibition of this institute will be held on Thursday and Friday, Dec. 4 and 5, at Church House, Westminster, London, S.W.1. The subjects chosen for discussion include subarachnoid hæmorrhage, chronic bronchitis and emphysema, treatment of carcinoma by supervoltage radiation, and radioisotope techniques. Further particulars may be had from the general secretary of the institute, 32, Welbeck Street, W.1.

Parkes Weber Collection

Dr. F. Parkes Weber, who is now 95, has presented to the Wellcome Historical Medical Library the collection of manuscript notes, reprints, and case-reports of rare diseases which he has brought together in the course of his career as a physician and medical writer. His books, *Rare Diseases and Some Debatable Subjects* (2nd ed., 1947) and *Further Rare Diseases* (1949), were based on a selection of this material. A general index to the collection will be prepared by the Wellcome Library, where it may be consulted in due course (together with the original records and reports) by all who are interested.

International Association of Gerontology

The European clinical section of this society will hold its first meeting in Sunderland from Oct. 1 to 4. The subjects chosen for discussion are genitourinary disturbances in old age, ageing and arteriosclerosis with particular reference to anticoagulant therapy, and confusional states in the elderly. Further particulars may be had from the hon. secretary, Dr. E. Woodford-Williams, The General Hospital, Sunderland.

The annual dinner of the Glasgow University Graduates in Yorkshire will be held at Leeds University on Friday, Oct. 17. Further particulars may be had from Mr. James Wishart, 33, Manor Row, Bradford, 1.

The London Hospital old students' dinner will be held at the Trocadero, Piccadilly, W.1, on Thursday, Oct. 9, at 7.45 P.M. Tickets (37*s.* 6*d.*, or 27*s.* 6*d.* for those qualified less than five years) may be had from Dr. R. R. Bomford, London Hospital, E.1.

The annual students' dinner of Leeds School of Medicine will be held on Friday, Oct. 31, at 7.30 P.M., in the Griffin Hotel, Boar Lane, Leeds, when Dr. F. F. Hellier will be in the chair.

Semipermanent exhibitions will be held at the Institute of Dermatology, Lisle Street, London, W.C.2, during the winter. The first, from Oct. 1 to 28, by Dr. J. P. O'Brien, will be on the sweat-retention syndrome.

The second number of the *Cerebral Palsy Bulletin* (summer, 1958) contains the late Dr. H. C. Cameron's last article, in which he discusses spasticity and the intellect. As an example of a spastic of brilliant intellect he cited Lord Byron, whose lameness Dr. Cameron believed to be due, not to a club-foot, but to spastic paraplegia. He effectively supported this retrospective diagnosis by contemporary descriptions of Byron's gait. Copies of the Bulletin (*2s. 6d.*) may be had from the secretary of the society, 28, Fitzroy Square, London, W.1.

From Monday, Oct. 13, the address of the South West Metropolitan Regional Hospital Board will be 40, Eastbourne Terrace, London, W.2.

CORRIGENDA: *Chlorpropamide.*—In last week's letter by Dr. Joan Walker (p. 641) we erroneously reproduced the start of the second sentence of the second paragraph as "43 diabetics had chlorpromazine . . ." This should have read: "43 patients had chlorpropamide . . ."

Accidental Hypothermia.—In Dr. Moylan's letter on this subject last week, a reference to Dr. Emslie-Smith's case 7 was inadvertently omitted and it should be made clear that Dr. Moylan's comparison was with this case only. His remarks on the inclusion of endogenous myxœdema hypothermia under the heading "accidental" similarly referred to case 7 only.

Appointments

CARRICK, JESSIE D., M.B. St. And.: assistant M.O. (maternity and child welfare), Cleethorpes area of Lindsey.
CONNOLLY, R. C., F.R.C.S.: surgeon, department of neurological surgery, St. Bartholomew's Hospital, London.
COOPER, P. R., B.M. Oxon., D.P.H., D.T.M.: senior M.O., London Airport.
CRAFT, M. J., M.D. Lond., M.R.C.P., D.P.M.: consultant psychiatrist to be designated medical superintendent, Balderton Hospital, near Newark.
EARL, C. J., M.D. Lond., M.R.C.P.: physician, National Hospital, Queen Square, London.
GINEVER, DOREEN M., M.B. Manc.: assistant M.O. and school M.O., Horsforth, near Leeds.
GOULD, W. L. P., L.M.S.S.A.: assistant M.O., Monmouthshire refraction unit.
MAIR, W. G. P., M.D. Aberd.: pathologist, National Hospital, Queen Square, London.
RAMSAY, W. W., M.B. Belf., D.Obst., D.P.H.: assistant M.O.H. and school M.O., Gloucestershire.
RAPER, A. B., M.D., B.SC. Leeds, M.R.C.P., D.T.M. & H.: pathologist, United Bristol Hospitals.
TOWNSEND, MARY, M.B. Lond., M.R.C.P., D.C.H.: assistant M.O., Halifax.
WHITFIELD, AUDREY P., M.B. Lond.: principal M.O., London Airport.

Colonial Appointments

BASSEY, E. E., L.S.M. Nigeria: medical superintendent, federal medical department, Federation of Nigeria.
FENDALL, N. R. E., M.D., B.SC. Lond., D.T.M. & H.: A.D.M.S., Kenya.
HUMPHREYS, J. R. H., M.B. Lond., M.O., North Borneo.
MCKENDRICK, A. J., M.B. Glasg., D.P.H., D.M.R.D.: specialist radiologist, Tanganyika.
SINCLAIR, A. D., M.B. Aberd., F.F.A.R.C.S., D.A.: medical superintendent, Barbados.
TATTERSFIELD, J. F., M.B. Lond.: M.O., Uganda.
TECK KAM, NEN LING, M.B. Lond., F.R.C.S.: assistant orthopædic surgeon, Mauritius.
WILLIAMS, H. N., M.B. Durh.: M.O., S.P.H.S., Fiji.